NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental NDAs
Application Number(s)	208798-S08 and 208799-(b) (4)S21
Priority or Standard	Priority
Submit Date(s)	December 21, 2020
Received Date(s)	December 21, 2020
PDUFA Goal Date	June 21, 2021
Division/Office	Division of Pulmonology, Allergy and Critical Care/ Office of Inflammation and Immunology
Review Completion Date	July 9, 2021
Established/Proper Name	NDA 208798: Fluticasone propionate (Fp) NDA 208799: Fluticasone propionate/salmeterol (FS)
(Proposed) Trade Name	Fp: ArmonAir Respiclick FS: AirDuo Respiclick and Digihaler
Pharmacologic Class	Fp: Inhaled corticosteroid FS: Inhaled corticosteroid and long-acting beta-agonist
Code name	
Applicant	Teva Branded Pharmaceutical Products
Dosage form	Dry powder inhaler
Applicant proposed Dosing Regimen	NDA 208798-S08 (Fp): 30 mcg and 55 mcg inhaled BID (b) (4) NDA 208799-S21 (FS): 55/14 mcg inhaled BID
Applicant Proposed Indication(s)/Population(s)	NDA 208798-S08 (Fp) (b) (4) Treatment of asthma in patients 4 years and older NDA 208799-S21 (FS): no change in proposed indication/ population
Recommendation on Regulatory Action	NDA 208798-S08 (Fp): Approval (b) (4) NDA 208799-S21 (FS): Approval
Recommended Indication(s)/Population(s) (if applicable)	NDA 208798-S08 (Fp): Treatment of asthma in 4 years and older (b) (4) NDA 208799-S21 (FS): Not applicable
Recommended Dosing Regimen	NDA 208798 S008 (Fp): One inhalation of FP 30 mcg or 55 mcg twice daily by oral inhalation

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Ngoc-Linh Do, PharmD
Office of Clinical Pharmacology Reviewer(s)	Lei He, PhD
Office of Clinical Pharmacology Team Leader(s)	Yunzhao Ren, MD, PhD
Clinical Reviewer	Sarah Zaidi, MD
Clinical Team Leader	Robert Lim, MD
Statistical Reviewer	Mingyu Xi, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Robert Lim, MD
Deputy Division Director (DPACC)	Banu Karimi-Shah, MD
Associate Division Director (OB)	Guoxing Soon, PhD
Office Director (or designated signatory authority)	Banu Karimi-Shah, MD

DPACC=Division of Pulmonolgy, Allergy, and Critical Care
OB=Office of Biostatistics

Additional Reviewers of Application

OPQ	Chong Ho Kim, PhD/Ramesh Raghavachari, PhD/ Zedong Dong, PhD
Microbiology	
OPDP	Taylor Burnett, PharmD, RAC
OSI	
OSE/DEPI	Sarah Vee, PharmD/ Idalia Rychlik, PharmD
OSE/DMEPA	
OSE/DRISK	
Other	Maria Nguyen, MSN, BSN, RN/ Marcia Williams

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Lei He	Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology	Sections: 6, 15.4	**Select one:** _ X _ Authored ___ Approved
	Signature: Lei He -S Digitally signed by Lei He -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lei He -S, 0.9.2342.19200300.100.1.1=2001209362 Date: 2021.07.08 13:10:48 -04'00'			
Clinical Pharmacology Team Leader	Yunzhao Ren	Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology	Sections: 6, 15.4	**Select one:** _X__ Authored _X _ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunzhao Ren -S, 0.9.2342.19200300.100.1.1=2000971048 Date: 2021.07.08 13:16:57 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Sarah Zaidi, MD	Office of Inflammation and Immunology (OII), Division of Pulmonology, Allergy and Critical Care (DPACC)	Sections: 1-4, 7-13, 15.2	**Select one:** _X__ Authored ___ Approved
	Signature: Sarah Zaidi -S Digitally signed by Sarah Zaidi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah Zaidi -S, 0.9.2342.19200300.100.1.1=2002325343 Date: 2021.07.09 09:02:31 -04'00'			
Clinical Team Leader	Robert Lim, MD	OII/DPACC	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Robert H. Lim -S Digitally signed by Robert H. Lim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert H. Lim -S, 0.9.2342.19200300.100.1.1=2000596695 Date: 2021.07.09 09:06:03 -04'00'			
Deputy Division Director (Clinical, Signatory Authority)	Banu Karimi-Shah, MD	OII/DPACC	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Banu A. Karimi-shah -S Digitally signed by Banu A. Karimi-shah -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300406057, cn=Banu A. Karimi-shah -S Date: 2021.07.09 09:11:54 -04'00'			
Statistical Reviewer	Mingyu Xi	Division of Biometrics III, Office of Biostatistics	Sections: 8.1, 8.3, 8.4	**Select one:** _x__ Authored _x__ Approved
	Signature: Mingyu Xi -S Digitally signed by Mingyu Xi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mingyu Xi -S, 0.9.2342.19200300.100.1.1=2001034850 Date: 2021.07.08 13:26:24 -04'00'			
Statistical Team Leader	Yongman Kim	Division of Biometrics III, Office of Biostatistics	Sections: 8.1, 8.3, 8.4	**Select one:** _x__ Authored _x__ Approved
	Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531 Date: 2021.07.08 14:33:53 -04'00'			
Associate Division Director (OB)	Guoxing Soon	Division of Biometrics III, Office of Biostatistics	Sections: 8.1, 8.3, 8.4	**Select one:** ___ Authored _x__ Approved
	Signature: Guoxing Soon -S Digitally signed by Guoxing Soon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guoxing Soon -S, 0.9.2342.19200300.100.1.1=1300124920 Date: 2021.07.08 21:09:03 -04'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Fluticasone Propionate (Fp) Multidose Dry Powder Inhaler (MDPI) (NDA 208798-S08)

The proposed drug product, Fp MDPI, is a fixed-dose inhaled corticosteroid (ICS) delivered in Teva's multidose dry powder inhaler (MDPI) currently approved for the treatment of asthma in patients ≥12 years of age at doses of 55, 113, and 232 mcg twice daily. These doses are administered as one inhalation twice daily. In this submission, the Applicant proposes to expand the indication to include patients 4 to 11 years old at the proposed doses of 30 mcg and 55 mcg twice daily. To support expansion of the indicated age range, the Applicant has submitted results from safety/efficacy trial trial FSS-AS-30003 (Trial 30003) and pharmacokinetic trial FSS-PK-10007 (Trial 10007).

Fluticasone Propionate/Salmeterol (FS) Multidose Dry Powder Inhaler (MDPI) (NDA 208799-(b) (4)S21)

The proposed drug product, FS MDPI, is a fixed-dose combination inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) delivered in Teva's multidose dry powder inhaler (MDPI) currently approved for the treatment of asthma in patients ≥12 years of age at fluticasone propionate/salmeterol doses of 55/14, 113/14, and 232/14 mcg twice daily. These doses are administered as one inhalation twice daily. In this submission, (b) (4) he Applicant has submitted results from safety/efficacy trial FSS-AS-30003 (Trial 30003) and pharmacokinetic trial FSS-PK-10007 (Trial 10007).

1.2. Conclusions on the Substantial Evidence of Effectiveness

(b) (4)

The regulatory action to be taken for FS 55/14 mcg NDA 208799-S21 is Approval.

The regulatory action to be taken is Approval for Fp for the treatment of asthma in 4 to 11-year olds at the doses of Fp 30 mcg orally inhaled BID and Fp 55 mcg orally inhaled BID (NDA 208798-S08).

To support these supplemental NDAs, the Applicant has submitted results from Trial 30003, a 12-week randomized, double-blind, placebo-controlled, parallel group trial in 841 patients aged 4 to 11 years old with persistent asthma. Trial 30003 was conducted to fulfill PREA requirements for NDA 208798 (3154-2) and NDA 208799 (3155-2) and to fulfill a Written Request. For the first co-primary endpoint of change from baseline in 1-hour post-dose FEV1 at

12-weeks for FS 55/14 mcg versus fluticasone propionrate (Fp) 55 mcg comparison, to demonstrate the contribution of the salmeterol monocomponent to the combination, results were not statistically significant. Results across all secondary endpoints for the FS 55/14 mcg to Fp 55mcg comparison wereconsistent with the first co-primary endpoint. These data suggest that the salmeterol monocomponent does not contribute to the effect of FS 55/14mcg in terms of efficacy. (b) (4) data from Trial 30003 are insufficient to support the efficacy of FS 55/14mcg.

With regard to the second co-primary endpoint of change from baseline in the weekly average of trough percent predicted FEV1 (tFEV1) of Fp 55 mcg compared to placebo, results demonstrated that treatment with Fp 55 mcg demonstrated improvements compared to placebo. While the 95% CI excluded null and the nominal p-value was <0.05, this result cannot be considered statistically significant due to failure earlier in the analysis hierarchy. Secondary endpoint results for Fp 55mcg were consistent with the second co-primary endpoint with the majority demonstrating that Fp 55mcg treatment resulted in numerically greater improvements versus placebo with 95% CIs excluding null. Results for the Fp 30 mcg versus placebo comparison mirrored the Fp 55 mcg results. While results for the Fp doses cannot be considered statistically significant, they are strongly suggestive of efficacy. As such, data from this trial, taken together with the clear efficacy previously demonstrated for Fp in the adolescent/adult program, is sufficient to support the efficacy of Fp 30 mcg and 55mcg in the 4 to 11-year-old population.

Pharmacokinetic Trial 10007, another PREA PMR trial for NDA 208798 (3154-1) and NDA 208799 (3155-1) was also submitted with these sNDAs. This trial which compared systemic exposures of Fp and FS to the approved Advair product, demonstrated that exposure to fluticasone propionate and salmeterol were comparable or lower to in patients administered Fp 55 mcg and FS 55/14 mcg as compared to Advair.

With regard to safety, no new safety signals were identified. These two trials have satisfied PREA PMRs issued at the initial approvals. Trial 30003 also fulfilled the Written Request.

The overall risk-benefit assessment of FS 55/14 mcg does not support the use of FS 55/14 mcg in 4 to 11-year olds with persistent asthma as the contribution of the salmeterol component was not demonstrated. (b) (4)

While trial results did not provide substantial evidence of efficacy for FS 55/14mcg in patients 4 to 11 years of age, Trial 30003 was a PREA PMR trial. Therefore, section 8.4 of the FS label will be amended to state that the safety and efficacy of FS 55/14 mcg has not been demonstrated in the 4 to 11 year old population. (b) (4) and the addition of pediatric data to section 8.4 will be taken under sNDA 208799-S21, as a labeling supplement with clinical data.

The overall risk-benefit assessment supports approval of Fp 30 mcg and Fp 55 mcg in the

maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. The regulatory action to be taken for the Fp 30 mcg and Fp 55 mcg sNDA 208798-S08 is Approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Fluticasone Propionate (Fp) Multidose Dry Powder Inhaler (MDPI), a fixed-dose inhaled corticosteroid (ICS) is currently approved for the maintenance treatment of asthma in patients ≥12 years of age at doses of 55, 113, and 232 mcg administered as one inhalation twice daily (NDA 208798). Fluticasone Propionate/Salmeterol (FS) Multidose Dry Powder Inhaler (MDPI), a fixed-dose combination of an inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), is currently approved for the maintenance treatment of asthma in patients ≥12 years of age at doses of 55/14, 113/14, and 232/14 mcg administered as one inhalation twice daily (NDA 208799). At the time of initial approval PREA PMRs were issued for patients 4-11 years of age. In thes supplemental NDAs, the Applicant has submitted results from Trial 30003, a 12-week randomized, double-blind, placebo-controlled, parallel group trial in 841 pediatric patients ages 4 through 11 years with persistent asthma to support the use of (b) (4) Fp 55 mcg and Fp 30 mcg administered twice daily in 4 to 11 year old patients with asthma. Results from Trial 10007, a pharmacokinetic study to compare systemic exposures of Fp and FS to Advair, were also submitted. These two pediatric studies were conducted to fulfill PREA requirements for both Fp and FS.

Asthma is a common, chronic respiratory disease. Asthma symptoms are caused by inflammation and narrowing of small airways and may include shortness of breath, coughing, wheezing, and chest pain. Disease severity ranges from mild with occasional symptoms to severe with persistent symptoms that impact quality of life. In the US, asthma affects more than 22 million persons and is one of the most common chronic diseases of childhood, affecting more than 6 million children. According to the CDC, in 2020, asthma affected 8% of the population in the United States, with the prevalence in children 5 years to 11 years old slightly higher than in adults (8.1 versus 7.7 percent). According to the CDC, in 2016 asthma-related physician office visits were 307.8 per 10,000, asthma-related emergency department visits were roughly 1600 per 10,000 and asthma-related hospitalizations were 5.9 per 10,000. This demonstrates the impact that asthma has on health in the United States. As a class, ICS are considered the most effective inhaled anti-inflammatory treatments for all severities of asthma across all age groups, including children younger than 11 years old. Guidelines for diagnosis and treatment of asthma in children over the age of 5 years are generally similar to those used and recommended for adults with a tailored stepwise approach to achieving asthma control. Generally, for asthma that is not adequately controlled on ICS, an ICS/LABA is recommended. Fluticasone propionate as Flovent and fluticasone

propionate/salmeterol as Advair have been approved in the 4-11-year-old asthma population since 2006 (fluticasone propionate) and 2004 (Advair).

In the efficacy analysis of Trial 30003, results from the analysis of the first co-primary endpoint of change from baseline in 1-hour post-dose FEV1 at 12-weeks for FS 55/14 mcg versus Fp 55 mcg comparison, which was meant to demonstrate the contribution of the salmeterol monocomponent to the combination, were not statistically significant [difference versus placebo 1.9 (p=0.285)]. Results across all secondary endpoints for the FS 55/14 mcg to Fp 55 mcg comparison were consistent with the first co-primary endpoint. These data suggest that the salmeterol monocomponent does not contribute to the effect of FS 55/14 mcg in terms of efficacy. (b) (4) data from Trial 30003 are insufficient to support the efficacy of FS 55/14 mcg. For the second co-primary endpoint, the change from baseline in weekly average of the trough morning ppFEV1 at week 12, the Fp 55 mcg versus placebo treatment difference was 7.0 with a 95% CI excluding null and the Fp 30 mcg versus placebo treatment difference was 6.0 with a 95% CI excluding null. Although this demonstrates evidence of a nominal positive treatment effect, due to the hierarchal testing strategy and failure to meet the first co-primary endpoint, results for the second co-primary endpoint and all secondary endpoints were not considered statistically significant. Secondary endpoint results for Fp 55 mcg were consistent with the second co-primary endpoint with the majority demonstrating that Fp 55 mcg treatment resulted in numerically greater improvements versus placebo with 95%CIs excluding null. Results for the Fp 30 mcg versus placebo comparison mirrored the Fp 55 mcg results. As such, data from this trial, taken together with the clear efficacy previously demonstrated for Fp in the adolescent/adult program, are sufficient to support the efficacy of Fp 30mcg and 55mcg in the 4 to 11-year-old population.

The safety data submitted with this supplemental NDA was sufficient to assess the safety of Fp and FS in the proposed patient population. The safety information for Fp and FS in 4 to 11-year-old patients is based on Trial 30003. No deaths occurred. Eight patients had nine serious adverse events during Trial 30003. The serious treatment emergent adverse events are typical of the patient population. There were a total of 8 treatment discontinuations due to adverse events in Trial 30003, that did not raise a safety concern. The SAE and AE profiles are typical for the population studied and consistent with the known safety profile of FP and FS. Overall, no new safety signals were identified for FP and FS.

Trial 10007, compared systemic exposures of Fp and FS to the approved Advair product, and demonstrated that exposure to fluticasone propionate and salmeterol were comparable or lower to in patients administered Fp 55 mcg and FS 55/14 mcg compared to Advair.

In summary, the regulatory action to be taken is Approval for Fp for the treatment of asthma in 4 to 11 year olds at the doses of Fp 30 mcg orally inhaled BID and Fp 55 mcg orally inhaled BID. (b) (4) .

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma, especially in the context of poorly controlled asthma. Severe exacerbations require emergency medical care and may even lead to hospitalization or death.	Asthma is a common condition. Patients can experience symptoms that are severe and life-threatening. Exacerbations can also impact patient's quality of life. Symptomatic control is important to protect against morbidity and mortality.
Current Treatment Options	Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations. There are several approved ICS and ICS/LABA products, though many are approved only for adults and adolescents.	Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations. ICS and ICS/LABA therapies are known to be effective treatment options for maintenance therapy.
Benefit	Based on the efficacy data for Trial 30003, the contribution of the salmeterol component to the FS combination product has not been demonstrated due to failure of the first co-primary endpoint and non-supportive secondary endpoint results for FS 55/14 mcg to Fp 55 mcg comparisons. For the second co-primary endpoint comparing Fp 55 mcg and Fp 30 mcg to placebo were not statistically significant due to failure of the first co-primary endpoint, the difference from placebo for both doses was favorable and nominally significant with 95%CI excluding the null. Secondary endpoints for Fp to placebo comparisons were consistent with the second co-primary endpoint. These data taken with the previously demonstrated efficacy of Fp in the ≥12 year old population are sufficient to support the efficacy of Fp in the 4 to 11 year old age group.	The evidence submitted by the Applicant to support pediatric approval in patients with asthma aged 4 to 11 years old has met the statutory evidentiary standard for providing substantial evidence of effectiveness for Fp 30 mcg and Fp 55 mcg. The evidence submitted by the Applicant (b) (4) in patients with asthma aged 4 to 11 years old has not met the statutory evidentiary standard for providing substantial evidence of effectiveness for FS 55/14 mcg.

Risk and Risk Management	The safety analysis of Trial 30003 did not raise any new safety concerns. Known safety issues for ICS and ICS/LABA products, such as Fp and FS include local effects such as oral candidiasis and systemic glucocorticoid effects including effects on growth. The most commonly reported treatment emergent adverse events occurred in the infections and infestations system organ class, with the most common preferred terms reported being nasopharyngitis, upper respiratory tract infection, and respiratory tract infection.	A comprehensive review of safety data did not reveal new safety concerns. The labeling for Fp and FS already include the known safety risks for ICS and ICS/LABA.

(b

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	C-ACT and asthma symptom scores are discussed in Section 8
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Asthma is a common, chronic respiratory disease. Asthma symptoms are caused by inflammation and narrowing of small airways and may include shortness of breath, coughing, wheezing, and chest pain. Disease severity ranges from mild with occasional symptoms to severe with persistent symptoms that impact quality of life. In the US, asthma affects more than 22 million persons and is one of the most common chronic diseases of childhood, affecting more than 6 million children. According to the CDC, in 2020, asthma affected 8% of the population in the United States, with the prevalence in children 5 years to 11 years old slightly higher than in adults (8.1 versus 7.7 percent). According to the CDC, in 2016 asthma-related physician office visits were 307.8 per 10,000, asthma-related emergency department visits were roughly 1600 per 10,000 and asthma-related hospitalizations were 5.9 per 10,000. This demonstrates the impact that asthma has on health in the United States. As a class, ICS are considered the most effective inhaled anti-inflammatory treatments for all severities of asthma across all age groups, including children younger than 11 years old. Inhaled corticosteroids allow for the control of asthma symptoms, improvement in lung function and decreased airway hyper-responsiveness. Guidelines for diagnosis and treatment of asthma in children over the age of 5 years are generally similar to those used and recommended for adults with a tailored stepwise approach to achieving asthma control. Generally, for asthma that is not adequately controlled on ICS, an ICS/LABA is recommended. Fluticasone propionate as Flovent and fluticasone propionate/salmeterol as Advair have been approved in the 4-11-year-old asthma population since 2006 (fluticasone propionate) and 2004 (Advair). Disease severity ranges from mild with occasional symptoms to severe with persistent symptoms that impact quality of life. However, even people with mild disease may suffer severe attacks.[1]

A sudden worsening of symptoms is known as an exacerbation. These often lead to missed days of work or school, urgent medical appointments, increased therapy, and occasionally hospitalization. US patients miss 10.5 million school days and 14.2 million workdays annually from asthma. Each year, asthma causes 1.75 million emergency department visits and 456,000 hospitalizations in the US.[2]

Asthma can present in a variety of ways, from early-onset childhood asthma with allergies, to late-onset adult non-allergic asthma associated with obesity. In allergic asthma, exposure of the

[1] Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, Liu X. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief* 2012: 1-8.

[2] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.

airway to allergens following sensitization causes mast cell degranulation and initiation of an inflammatory cascade. In non-allergic asthma, epithelial stimulation and initiation of inflammation can occur with viral or bacterial infections or exposure to noxious chemicals.[3]

Diagnosis is based on the pattern of symptoms, response to therapy over time, and spirometry. Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate.[4]

2.2. Analysis of Current Treatment Options

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agonists (LABAs) with concurrent ICS, combination inhaled corticosteroids and long-acting bronchodilators (ICS/LABA), a combination inhaled corticosteroid, long-acting beta agonist, and long-acting muscarinic antagonist (ICS/LABA/LAMA), leukotriene modifying drugs, methylxanthines, inhaled anticholinergics, anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, anti-IL5 receptor antibody benralizumab, anti-IL4 receptor antibody dupilumab, and anti-IgE antibody omalizumab. Historically, ICSs are considered to be the most effective treatment for persistent asthma and are used as the first drug when a maintenance treatment is necessary. When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is often added, preferably for a limited time period with the intent of discontinuing the LABA if asthma control is achieved and maintained. In 2019, the Global Initiative for Asthma (GINA) treatment guidelines changed to advise the use of a combination of ICS-formoterol as rescue medication for as-needed use in mild intermittent asthma and in worsening asthma across all severities. It also advised as-needed ICS-formoterol as an alternative to daily low-dose ICS for persistent asthma (step 2). In 2020, the National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-3 (EPR-3) incorporated the use of ICS-formoterol as advised in GINA to the US Asthma Management Guidelines.[5] Since some patients with asthma use both an ICS and a LABA, these two drugs have been combined together in the same formulation and in the same device and marketed as combination products. There are several such combination products in the market in the United States. Examples include Advair Diskus and Advair HFA Inhalation Aerosol (both are a combination of fluticasone propionate and salmeterol), Symbicort (a combination of budesonide and formoterol fumarate), Dulera (a combination of mometasone furoate and formoterol

---

[3] Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R, Jr., Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER, National Heart L, Blood Institute's Severe Asthma Research P. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181: 315-323.

[4] Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. 2020 [Accessed January 15, 2021]. Available from: http://www.ginasthma.org.

[5] 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group

fumarate), and Breo Ellipta (a combination of fluticasone furoate and vilanterol).

Corticosteroids administered systemically at large doses have variety of serious adverse effects that are well known. Although ICS do not usually have the typical serious adverse effects associated with systemic corticosteroids because absorption from the inhaled route is limited, ICS are known to have systemic effects, such as changes in bone mineralization and an effect on linear growth in young growing children. ICS also have local adverse effects, such as oral candidiasis, and pneumonia in patients with COPD, particularly at high doses.

Current medications approved for asthma are shown in Table 1.

Table 1. Approved Asthma Medications

Class	Generic Name	Brand Name	Year Approved
Long-Term Control Medications			
Inhaled corticosteroids	Beclomethasone dipropionate HFA	Qvar	2002
	Budesonide	Pulmicort	1997
	Ciclesonide	Alvesco	2008
	Fluticasone furoate	Arnuity Ellipta	2014
	Fluticasone propionate	Flovent	1996
	Mometasone DPI/HFA	Asmanex	2005
Combination inhaled corticosteroids/long-acting bronchodilator (ICS/LABA)	Budesonide/formoterol	Symbicort	2006
	Fluticasone/salmeterol	Advair	2000
	Mometasone/formoterol	Dulera	2010
	Fluticasone/vilanterol	Breo Ellipta	2015
Anticholinergics	Tiotropium	Spiriva	2015
Combination inhaled corticosteroids/long-acting bronchodilator/long-acting muscarinic antagonist (ICS/LABA/LAMA)	Fluticasone furoate/umeclidinium/ vilanterol	Trelegy Ellipta	2020
Leukotriene modifiers	Montelukast	Singulair	1998
	Zafirlukast	Accolate	1996
	Zileuton	Zyflo	1996
Biologics	Omalizumab	Xolair (anti-IgE)	2003
	Mepolizumab	Nucala (anti-IL5)	2015
	Reslizumab	Cinqair (anti-IL5)	2016
	Benralizumab	Fasenra (anti-IL5R)	2017
	Dupilumab	Dupixent (anti-IL4R)	2018
Xanthines	Theophylline	Multiple	

Class	Generic Name	Brand Name	Year Approved
Rapid Relief Medications			
Short-acting beta$_2$-adrenergic agonists (SABAs)	Albuterol Sulfate	ProAir Proventil Ventolin Vospire ER	1981
	Levalbuterol	Xopenex	1999

Source: Drugs@FDA, accessed on May June 1, 2021, available at https://www.accessdata.fda.gov/scripts/cder/daf/
Abbreviations: DPI, dry powder inhaler; ER, extended release; HFA, hydrofluoroakane; ICS, inhaled corticosteroid; Ig, immunoglobulin; IL, interleukin; LABA, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta$_2$-adrenergic agonist

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fluticasone propionate as Teva's ArmonAir Respiclick and fluticasone propionate/salmeterol as Teva's AirDuo RespiClick and Digihalers were initially approved on January 27, 2017 in patients ≥12 years of age.

3.2. Summary of Presubmission/Submission Regulatory Activity

Interactions relevant to this supplemental NDA are summarized here. At initial approval pediatric studies under PREA were waived for the <4-year-old population and two PREA Postmarketing Requirement (PMR) studies were issued. One was a 3-period, crossover study to determine the pharmacokinetic (PK) profile and tolerability of single doses of fluticasone propionate (Fp) inhalation powder multi-dose dry powder inhaler (MDPI) and fluticasone propionate/salmeterol xinafoate (FS) inhalation powder MDPI compared to Advair Diskus in patients with persistent asthma 4 through 11 years of age. The other was a 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of fluticasone propionate inhalation powder multidose dry powder inhaler (MDPI) compared with fluticasone propionate/salmeterol xinafoate inhalation powder MDPI in patients with persistent asthma 4 through 11 years of age. The PREA PMR studies were identical between Fp NDA 208798 and FS NDA 208799 except for the number designation. For NDAs 208798 the PREA PMR studies were designated 3154-1 and 3154-2 for the PK/safety study and safety/efficacy study, respectively. For the FS NDA 208799, the studies were designated 3155-1 and 3155-2.

A pediatric Written Request (WR) was also issued on November 17, 2017. The trial included in the pediatric WR was based on PMR 3154-2 and 3155-2 and was a randomized, placebo-controlled, double-blind, parallel-group, 12-week study of two doses (30 and 55 mcg twice daily) of fluticasone propionate multi-dose dry powder inhaler, one dose of fluticasone propionate/salmeterol (55/14 mcg twice daily), and placebo. The objective of the trial was to evaluate the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol multi-dose dry powder inhaler in pediatric patients ages 4 to 11 years with persistent asthma. The primary efficacy endpoint was to include the change from baseline in weekly average of the percent predicted trough morning FEV1 at Week 12 for fluticasone propionate multi-dose dry powder inhaler compared to placebo and the change from baseline in 1-hour post-dose percent predicted morning FEV1 at Week 12 for fluticasone propionate/salmeterol compared to fluticasone propionate. Other efficacy variables were to include spirometry, asthma symptom scores, asthma control, use of reliever medication, and the number of withdrawals for asthma exacerbation. Safety variables were to include adverse events, discontinuations due to adverse events, serious adverse events, vital signs (blood pressure and pulse), and physical examinations including oropharyngeal examinations.

The WR was amended multiple times to extend the clinical trial report submission deadline to December 31, 2020, as well as to include the metered doses of the approved products. The

protocol was also amended on June 27, 2018 to increase the sample size from (b) (4) patients after blinded data monitoring (b) (4) than initially assumed.

A pre-sNDA meeting held with the Applicant on Oct 15, 2019 to discuss results from the Trial 30003. Relevant discussion points included the following:

- FS trial data were not convincing at preliminary review as the comparison to Fp were not statistically significant for the first co-primary endpoint; and the contribution of salmeterol to the combination was not demonstrated.
- To better support the efficacy of FS, the Applicant was advised to conduct an additional trial that could potentially be shorter than the completed trial, not necessarily placebo controlled, use clinic assessed spirometry, and potentially include pre-specified Bayesian approaches to decrease sample size.
- With regard to Fp, while there were multiplicity issues given failure of the FS to Fp comparison, Fp comparisons versus placebo were for the second co-primary, pending review could potentially support an sNDA submission for Fp.
- Home spirometry data acceptability would be a review issue.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No sites were inspected due to the low safety concern and the ongoing novel coronavirus SARS-CoV-2 pandemic.

4.2. Product Quality

The Chemistry, Manufacturing and Controls (CMC) review team recommended Approval for these efficacy supplemental NDAs from the CMC standpoint. For details please refer to the CMC review dated April 6, 2021. The executive summary of the CMC review is as follows:

1) To support the registration of Fp MDPI 30 mcg, Teva has provided characterization data for the (b) (4) scale registration/clinical batches (3.2.P.2.4. Drug Product Characterization Studies – Summary – 30 mcg). In addition, Teva has also provided the available stability data for three 30 mcg batches manufactured at (b) (4) (up to 24 months and in-use stability for Batch RD1014 and RD1119, 1 month accelerated and 2 months in-use for AFR95A):

- Teva's claim for a categorical exclusion from the requirement of an Environmental Assessment is fully justified.
- Dose proportionality is demonstrated for DCU, FPF and for APSD.
- The drug product appears well-characterized.
- Overall Manufacturing Inspection Recommendation is "APPROVE" (dated March 22, 2021).
- Teva's proposal of a 24 month expiration dating period for the Fp MDPI 30 mcg, 60 actuation drug product when stored with its protective packaging intact in either the upright or inverted orientation is acceptable.

(b) (4)

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No new device data were submitted in this supplemental NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data were provided in this supplemental NDA.

6 Clinical Pharmacology

6.1. Executive Summary

On December 21, 2020, Teva submitted the following pediatric supplements seeking approval of ArmonAir RespiClick/Digihaler [ArmonAir, fluticasone propionate (Fp) dry powder inhaler (MDPI)] (b) (4) in younger children with asthma.

- NDA 208798-S08 for ArmonAir :
  - The proposed indication: for the maintenance treatment of asthma as prophylactic therapy in pediatric patients 4 to 11 years of age
  - The proposed dosing regimen: 1 inhalation, 30 mcg or 55 mcg twice daily

(b) (4)

The submissions are to fulfill two pediatric Post-Marketing Requests (PMRs) issued in the approval letters of NDA 208798 (3154-1 and 3154-2) and NDA 208799 (3155-1 and 3155-2) on January 27, 2017:

- PMR 3154-1/3155-1: Conduct a double-blind (incorporating an open-label comparator), 3-period, crossover study to determine the pharmacokinetic profile and tolerability of single doses of fluticasone propionate inhalation powder multi-dose dry powder inhaler (MDPI) and fluticasone propionate/salmeterol xinafoate inhalation powder MDPI compared to Advair Diskus in patients with persistent asthma 4 through 11 years of age.

- PMR 3154-2/3155-2: Conduct a 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of fluticasone propionate inhalation powder multi-dose dry powder inhaler (MDPI) compared with fluticasone propionate/salmeterol xinafoate inhalation powder MDPI in patients with persistent asthma 4 through 11 years of age.

The clinical development program for Fp MDPI and FS MDPI in children aged 4 through 11 years includes two clinical studies:

- Study FSS-PK-10007 is a double-blind (incorporating an open-label comparator), 3-Period, crossover study to determine the PK and tolerability following single dose of Fp

MDPI, FS MDPI, and ADVAIR® DISKUS® in patients with persistent asthma 4 through 11 Years of Age.

- Study FSS-AS-30003 is a randomized, double-blind, placebo-controlled, efficacy and safety study following 12-week treatment of Fp MDPI, FS MDPI, or placebo.

PK result of Study FSS-PK-10007 indicates that the AUC_{0-t} and C_{max} values of Fp following a single dose of ArmonAir 55 mcg are comparable to or slightly lower than that of ADVAIR DISKUS 100/50 mcg in pediatric patients with asthma 4 to 11 years of age.

PK result of Study FSS-PK-10007 indicates that the AUC_{0-t} and C_{max} values of Fp following a single dose of AirDuo 55/14 mcg are 40% and 52% lower than that of ADVAIR DISKUS 100/50 mcg, respectively, in pediatric patients with asthma 4 to 11 years of age. The AUC_{0-t} and C_{max} values of salmeterol following a single dose of AirDuo 55/14 mcg are 66% and 53% lower than that of ADVAIR DISKUS 100/50 mcg, respectively, in pediatric patients with asthma 4 to 11 years of age.

In addition, PK result of Study FSS-PK-10007 indicates that the AUC_{0-t} and C_{max} values of Fp following a single dose of AirDuo 55/14 mcg are approximately 35% lower than that of ArmonAir 55 mcg in pediatric patients with asthma 4 to 11 years of age. The result is inconsistent with result obtained in patients with asthma at least 12 years of age from Study FSS-AS-10042 included in the original NDA 208799 submission, which demonstrated that the systemic exposure of Fp is comparable between Fp MDPI 200 mcg and FS MDPI 200/12.5 mcg.

6.1.1. Recommendations

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) have reviewed the clinical pharmacology data submitted under sNDA. NDA208798-S08 pediatric supplement is approvable from a clinical pharmacology perspective. The proposed pediatric dose (i.e., 1 inhalation, 30 mcg or 55 mcg twice daily) is acceptable.

(b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Refer to the approved drug label of NDA 208798, the general clinical pharmacology information of Fp is listed below:

- Absorption
  Fp 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 Fp was negligible (<1%), primarily due to incomplete

absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the Fp delivered to the lung was systemically absorbed.

Following ArmonAir administration, the peak plasma concentration of Fp occurs at approximately 1 hour after inhalation. The mean peak concentration following a 232-mcg single oral inhalation of ArmonAir to patients 12 years and older with persistent asthma was 73 pg/mL.

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

  The percentage of Fp bound to human plasma proteins averages 99%. Fp 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 ARMONAIR RESPICLICK was approximately 11.2 hours.

  - Metabolism
    The total clearance of Fp 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.

- Specific Populations
  (b) (4)
  Patients with Renal Impairment: The effect of renal impairment on the PK of ArmonAir has not been evaluated.

  Patients with Hepatic Impairment: Formal PK studies using ArmonAir have not been conducted in patients with hepatic impairment. However, since Fp is predominantly

cleared by hepatic metabolism, impairment of liver function may lead to accumulation of Fp in plasma.

- Drug Interaction Studies
  In vitro and in vivo drug interaction studies have not been conducted with ArmonAir.

  Inhibitors of Cytochrome P450 3A4:
  Ritonavir: Coadministration of ritonavir with Fp aqueous nasal spray significantly 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 Fp (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma Fp exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

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

Refer to the approved drug label of NDA 208799, the general clinical pharmacology information of salmeterol is listed below:

- Absorption
  After administration of 232 mcg/14 mcg AirDuo to patients aged 12 years and older with persistent asthma, the mean C_{max} values of salmeterol was 60 pg/mL. The median tmax was (b) (4).

- Distribution
  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
  Terminal half-life estimates for salmeterol for AirDuo 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.

- Specific Populations
  The popPK analyses for Fp and salmeterol showed no clinically relevant effects of gender, race, body weight, body mass index, or percent of predicted FEV1 on apparent clearance and apparent volume of distribution.

  Patients with Renal Impairment: The effect of renal impairment on the PK of AirDuo has not been evaluated.

  Patients with Hepatic Impairment: Formal PK studies using AirDuo have not been conducted in patients with hepatic impairment. However, since salmeterol is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma.

- Drug Interaction Studies
  In a single-dose trial, the presence of salmeterol did not alter fluticasone propionate exposure.

  No studies have been performed with AirDuo to investigate the effect of Fp on salmeterol PK when given in combination.

  In a placebo-controlled, crossover drug interaction trial in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole, a strong CYP3A4 inhibitor, (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. Peak plasma salmeterol concentrations were increased by 1.4-fold. Three out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects. 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 administration alone and placebo administration.

  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 C_{max} 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.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

ArmonAir and AirDuo were originally approved under NDA208798 and NDA208799 on January 27, 2017, respectively, in patients 12 years of age and older:

- The approved dosing regimen of ArmonAir is 1 inhalation of 55 mcg, 113 mcg, or 232 mcg twice daily by oral inhalation
- The approved dosing regimen of AirDuo is 1 inhalation, 55/14, 113/14, or 232/14 mcg twice daily by oral inhalation

The proposed dosing regimen of pediatric patients 4 to less than 12 years of age are:

- ArmonAir RespiClick (Fp inhalation powder): 1 inhalation, 30 mcg or 55 mcg twice daily (b) (4)

Therapeutic Individualization

None

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Fp is a corticosteroid and salmeterol is a long-acting beta2-adrenergic agonist.

In these supplements, Teva submitted a study report of PK study FSS-PK-10007, entitled "A Double-Blind (Incorporating an Open-Label Comparator), 3-Period, Crossover Study to Determine the Pharmacokinetic Profile and Tolerability of Single Doses of Fluticasone Propionate Multidose Dry Powder Inhaler and Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler Compared to ADVAIR® DISKUS® in Patients with Persistent Asthma 4 through 11 Years of Age".

Study FSS-PK-10007 is a double-blind (incorporating an open-label comparator), randomized, 3-period crossover (7 (±2)-day washout period), single-dose study in patients with persistent asthma 4 through 11 years of age. Only patients who had documented correct use of the MDPI or DISKUS device on day -1 were eligible to take the active dose of study drug on day 1 in each

treatment period. 20 patients with persistent asthma were randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA) containing the following 3 treatments:

- Treatment A: Fp MDPI 55 mcg, 1 inhalation
- Treatment B: FS MDPI 55/14 mcg, 1 inhalation
- Treatment C: ADVAIR DISKUS (FS) 100/50 mcg, 1 inhalation

The to-be-marketed formulation and device for Fp MDPI and FS MDPI were used. Blood samples were collected in each treatment period at multiple timepoints as follows:

- In patients 4-5 years of age: predose, and post-dose at 5 (±1) and 20 (±1) minutes, 1 hour (±5 minutes), 4 hours (±5 minutes), and 8 hours (±5 minutes)
- In patients 6- 11 years of age: predose, and post-dose at 5 (±1) and 20 (±1) minutes, 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), and 8 hours (±5 minutes)

Plasma concentrations of Fp and salmeterol were simultaneously determined using a validated liquid chromatography-tandem mass spectrometry methods. Refer to Appendix 19.4 regarding details of the bioanalytical assay.

All randomized pediatric patients (n=20) received all assigned doses of study drug (Table 2). Plasma concentration data for Fp MDPI 55 mcg of 2 patients (Patient (b) (6) and Patient (b) (6)) were excluded in PK analysis because the predose concentration was >5% of C_{max}.

Table 2. Demographic Information of Patients in Study FSS-PK-10007 (ITT Population)

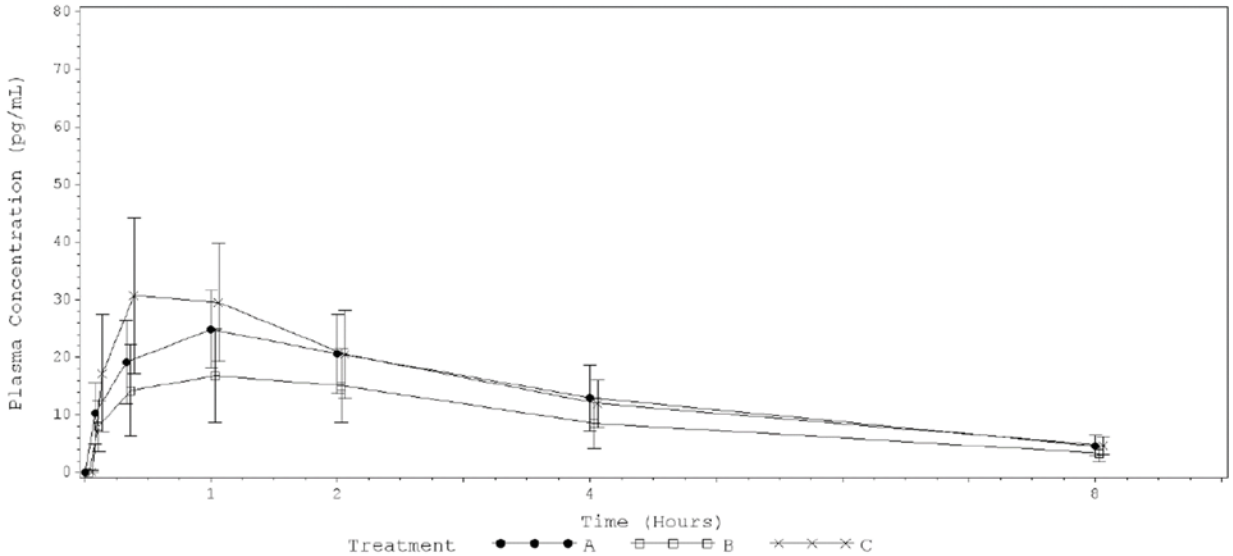
Variable Statistic	Total (N=20)
Age, years	
n	20
Mean (SD)	7.7 (2.54)
SE	0.57
Median (min, max)	8.5 (4, 11)
Sex, n (%)	
Male	8 (40)
Female	12 (60)
Race, n (%)	
White	14 (70)
Black	6 (30)
Ethnicity, n (%)	
Not Hispanic or Latino	12 (60)
Hispanic or Latino	8 (40)
BMI, kg/m^2	
n	20
Mean (SD)	18.124 (2.5612)
SE	0.5727
Median (min, max)	17.405 (14.65, 25.24)

Source: Table 4 of Study FSS-PK-10007 Clinical Study Report, page 50
Five patients were 4 through 5 years of age.
Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in study arm; n, number of subjects with indicated characteristic; SD, standard deviation

Fp PK results

Following a single oral inhalation of Fp MDPI 55 mcg, FS MDPI 55/14 mcg, or ADVAIR DISKUS 100/50 mcg, the mean plasma PK profiles and PK parameters of Fp are shown in Figure 1 and Table 3. Statistical analysis as shown in Table 4 indicated that Fp systemic exposure (AUC and C_{max}) with Fp MDPI 55 mcg or FS MDPI 55/14 mcg are comparable to or up to 52% lower than the Fp systemic exposure from ADVAIR DISKUS 100/50 mcg.

Figure 1. Plasma Concentration-Time Profiles of Fluticasone Propionate by Treatment (Linear Scale)



Source: Figure 3 of Study FSS-PK-10007 Clinical Study Report, page 56
Treatment A=Fp MDPI 55 mcg; Treatment B=FS MDPI 55/14 mcg; Treatment C=ADVAIR DISKUS 100/50 mcg
Data expressed as mean ± SD.
Abbreviations: Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; SD, standard deviation

Table 3. Summar of Plasma PK Parameters of Fluticasone Pro ionate b Treatment

Parameter Statistics	Fp MDPI 55 mcg[a] (50 mcg[b]) (N=18)	FS MDPI 55/14 mcg[a] (50/12.5 mcg[b]) (N=20)	ADVAIR DISKUS 100/50 mcg[c] (N=20)
AUC_{0-t} (h·pg/mL)			
n	18	20	20
Mean	110.65	74.19	119.09
Geometric mean	106.41	67.82	112.93
SD	34.122	34.422	38.960
Min, Max	69.08, 211.56	26.15, 186.99	57.47, 185.07
C_{max} (pg/mL)			
n	18	20	20
Mean	25.66	17.56	34.29
Geometric mean	24.80	15.58	32.31
SD	6.549	8.083	12.555
Min, Max	11.94, 38.00	3.70, 41.89	18.16, 66.52
t_{max} (h)			
n	18	20	20
Median	1.00	1.00	0.41
Min, Max	0.33, 2.00	0.33, 8.00	0.08, 1.00

Source: Table 2 of Summary of Clinical Pharmacology Studies, page 11
[a] Metered dose
[b] Nominal dose
[c] Metered dose for ADVAIR DISKUS
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; h, hour; Max, maximum; MDPI, multidose dry powder inhaler; Min, minimum; N, number of subjects in study arm; n, number of samples; PK, pharmacokinetic; SD, standard deviation; t_{max}, time to maximum concentration

Table 4. Summary of Fluticasone Propionate PK Comparison

Parameter	Treatment[a]	Geo LSM	GMR (90% CI)
AUC_{inf} (h*pg/mL)	Fp/FS	113.4/82.7	1.37 (1.10, 1.70)
	Fp/ADVAIR	113.4/132.6	0.85 (0.70, 1.05)
	FS/ADVAIR	82.7/132.6	0.62 (0.52, 0.75)
AUC_{0-t} (h*pg/mL)	Fp/FS	102.9/68.1	1.51 (1.30, 1.76)
	Fp/ADVAIR	102.9/113.4	0.91 (0.78, 1.06)
	FS/ADVAIR	68.1/113.4	0.60 (0.52, 0.70)
C_{max} (pg/mL)	Fp/FS	24.1/15.6	1.55 (1.26, 1.90)
	Fp/ADVAIR	24.1/32.3	0.75 (0.61, 0.92)
	FS/ADVAIR	15.6/32.3	0.48 (0.40, 0.59)

Source: Reviewer's analysis
[a] Fp: Fp MDPI 55 mcg (N=18); FS: FS MDPI 55/14 mcg (N=20); ADVAIR: ADVAIR DISKUS 100/50 mcg (N=20)
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time zero to the last measurable concentration; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; Geo LSM, geometric least squares mean; GMR, geometric mean ratio; MDPI, multidose dry powder inhaler; PK, pharmacokinetic

For the comparison of Fp systemic exposure between Fp MDPI and FS MDPI, Fp AUC and C_{max} with Fp MDPI 55 mcg are 51% and 55% higher than with FS MDPI 55/14 mcg, respectively. This may be interpreted that salmeterol reduces Fp systemic exposure by approximately half in children 4 to 11 years of age.

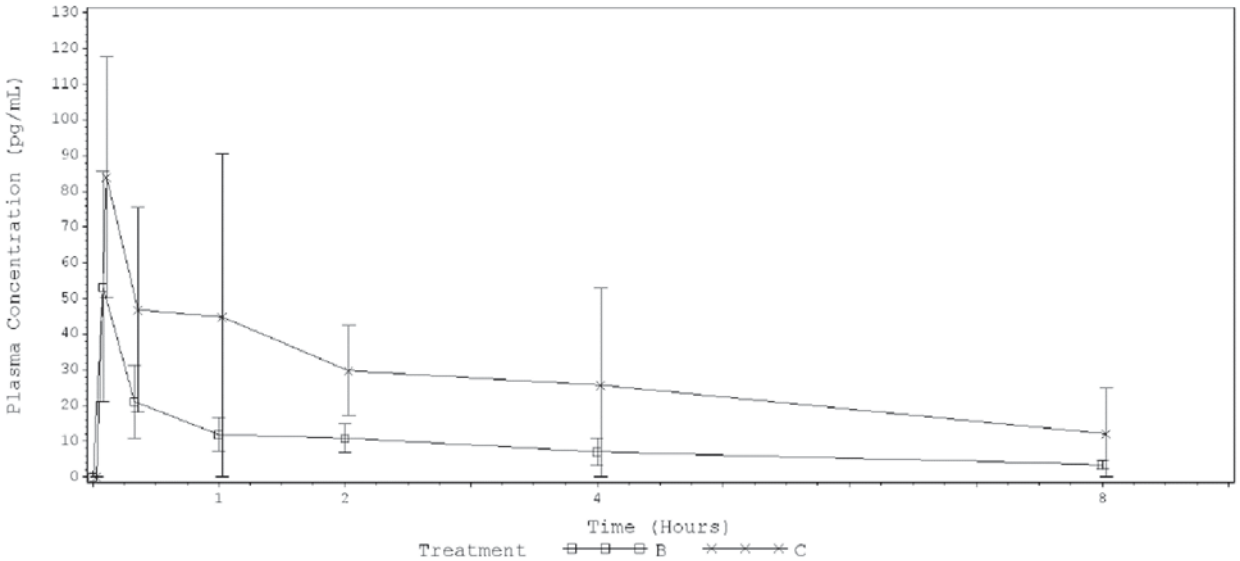
In the original NDA submissions for Fp MDPI and FS MDPI, a dedicated PK interaction study (FSS-AS-10042) in patients with asthma 12 years and older (n=43) showed that following the single dose administration of Fp MDPI (200 mcg×1 inhalation), FS MDPI (200/12.5 mcg×1 inhalation), and ADVAIR DISKUS (500/50 mcg×1 inhalation), the systemic exposure (C_{max}, AUC_{0-t}, and AUC_{0-inf}) of Fp is comparable between Fp MDPI and FS MDPI, suggesting the presence of salmeterol in FS MDPI does not affect Fp PK (refer to the Clinical Pharmacology Review dated October 28, 2016 by Dr. Lei He for more details).

The reason that causes discrepancy of the effect of salmeterol on Fp systemic exposure in patients 4 to 11 years of age and in patients 12 years and older is unclear, but the results should be interpreted with caution. Note that this pediatric PK study in subjects 4 to 11 years of age (FSS-PK-10007) was conducted in a small number of subjects (n=20) and the PK sampling schedule (up to 8 hours post-dose) was also sparser and shorter than Study FSS-AS-10042, by considering the reported terminal half-life of 11.2 hours of Fp following oral inhalation of ARMONAIR RESPICLICK in subjects 12 years and older.

Salmeterol PK results

Following a single oral inhalation of FS MDPI 55/14 mcg or ADVAIR DISKUS 100/50 mcg, the mean plasma PK profiles and PK parameters of salmeterol are shown in Figure 2 and Table 5. Statistical analysis as shown in Table 6 indicated that salmeterol AUC and C_{max} with FS MDPI 55/14 mcg are 66% and 53% lower, respectively, when compared to ADVAIR DISKUS 100/50 mcg.

Figure 2. Plasma Concentration-Time Profiles of Salmeterol by Treatment (Linear Scale)



Source: Figure 7 of Study FSS-PK-10007 Clinical Study Report, page 60
Treatment B=FS MDPI 55/14 mcg; Treatment C=ADVAIR DISKUS 100/50 mcg
Data expressed as mean ± SD
Abbreviations: Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; SD, standard deviation

Table 5. Summar of Plasma PK Parameters of Salmeterol b Treatment

Parameter Statistics	B: FS MDPI 50/12.5 mcg (N=20)	C: ADVAIR DISKUS 100/50 mcg (N=20)
AUC_{0-t} (h*pg/mL)		
n	20	20
Geometric mean	63.78	188.63
SD	30.142	206.116
Min, Max	10.81,131.78	71.62,872.79
C_{max} (pg/mL)		
n	20	20
Geometric mean	38.58	82.15
SD	31.699	42.977
Min, Max	1.59,128.74	25.27,207.52
t_{max} (h)		
n	20	20
Median	0.08	0.08
Min, Max	0.08,1.03	0.08,1.02

Source: Table 4 of Summary of Clinical Pharmacology Studies, page 62
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; h, hour; Max, maximum; MDPI, multidose dry powder inhaler; Min, minimum; N, number of subjects in study arm; n, number of samples; PK, pharmacokinetic; SD, standard deviation; t_{max}, time to maximum concentration
FS MDPI 50/12.5 mcg nominal dose is equivalent to 55/14 mcg metered dose

Table 6. Summary of Salmeterol PK Comparison

Parameter	Treatment[a]	Geo LSM	GMR (90% CI)
AUC_{inf} (h*pg/mL)	FS/ADVAIR	102.1/223.6	0.46 (0.33, 0.64)
AUC_{0-t} (h*pg/mL)	FS/ADVAIR	64.0/189.0	0.34 (0.25, 0.45)
C_{max} (pg/mL)	FS/ADVAIR	38.6/82.1	0.47 (0.31, 0.72)

Source: Reviewer's analysis
[a] FS: FS MDPI 55/14 mcg (N=20); ADVAIR: ADVAIR DISKUS 100/50 mcg (N=20)
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time zero to the last measurable concentration; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; FS, fluticasone propionate/salmeterol; Geo LSM, geometric least squares mean; GMR, geometric mean ratio; MDPI, multidose dry powder inhaler; PK, pharmacokinetic

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Refer to the clinical review and statistical review for more details regarding efficacy assessment.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The proposed management strategy for pediatric subjects 4 to 11 years of age based on intrinsic factors (i.e., monitor for systemic corticosteroid effects in patients with hepatic impairment) is consistent with the approved recommendations for subjects 12 years and older, which is reasonable. Refer to the approved drug labels of NDA 208298 and NDA 208799 for details.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The proposed management strategy for pediatric subjects 4 to 11 years of age regarding drug-drug interactions (i.e., avoid strong CYP3A4 inhibitors) is consistent with the approved recommendations for subjects 12 years and older, which is reasonable. Refer to the approved drug labels of NDA 208298 and NDA 208799 for details.

Question on clinically relevant specifications (TBD)?

None

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Trial 30003 was the primary source of clinical data used in this review to support safety/efficacy and is summarized in Table 7.

Table 7. Summary of Clinical Studies Included in This Submission to Support Safety/Efficacy

Trial Identity	NCT Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	Number of Patients Randomized	Study Population	Number of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
FSS-AS-30003	NCT02980133	Multicenter randomized double-blind parallel-group placebo-controlled trial	Fp 30 mcg BID Fp 55 mcg BID FS 55/14 mcg BID Placebo BID	Co-primary endpoints: CFB 1-hour post-dose ppFEV1 at week 12 and CFB weekly average of trough morning ppFEV1	12-week treatment duration with 7-day follow up	824	4-11 year-olds with persistent asthma	118 trial centers in the United States and Europe

Abbreviations: BID, twice daily; CFB, change from baseline; Fp, fluticasone propionate, FS, fluticasone propionate/salmeterol; NCT, National Clinical Trial; ppFEV1, percent predicted forced expiratory volume in 1 second

7.2. Review Strategy

Trial FS-AS-30003 is referred to in this review as Trial 30003 for brevity. Trial 30003 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of fluticasone propionate (FP) Multidose Dry Powder Inhaler (MDPI) 30 mcg and 55 mcg administered twice daily and fluticasone propionate/salmeterol (FS) Multidose Dry Powder Inhaler (MDPI) 55/14 mcg administered twice daily in patients aged 4 through 11 years old with persistent asthma. Note that Trial 10007 was also submitted with this sNDA and is reviewed in section 6 Clinical Pharmacology.

The protocol for Trial 30003 is discussed in Section 8.1.1, trial results in Section 8.1.2, and safety results in Section 8.2.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Number FSS-AS-30003 (Trial 30003)

Title and Administrative Information

Trial 30003 was titled "A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients Aged 4 Through 11 Years with Persistent Asthma." Trial 30003 was conducted at 118 centers US and worldwide from December 28, 2016 to April 13, 2019.

Objective

The primary objective was to evaluate the efficacy of Fp MDPI and FS MDPI when administered over 12 weeks in patients 4 through 11 years of age with persistent asthma.

Trial Design

This trial was a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of fluticasone propionate (Fp) Multidose Dry Powder Inhaler (MDPI) 30 mcg and 55 mcg administered twice daily and fluticasone propionate/salmeterol (FS) Multidose Dry Powder Inhaler (MDPI) 55/14 mcg administered twice daily in patients aged 4 through 11 years old with persistent asthma. Patients on stable asthma treatment who met trial participation criteria at screening visit had a 14- to 30-day run-in period to wash out their asthma and non-asthma disallowed medications. A short-acting bronchodilator (albuterol or salbutamol hydrofluoroalkane metered-dose inhaler) was given to all study patients for use as rescue medication. A maximum of 12 inhalations per day were permitted. The three periods of the trial consisted of patient-blinded run-in period (up to 30-days); double-blind treatment period (approximately 12-weeks); and a follow-up period (approximately 7 days after the end of the treatment period). All patients/guardians provided informed consent, and assent where applicable, prior to trial participation. Patients were provided 510-k cleared Asthma Monitor 3 (AM3) handheld spirometers at the screening visit. This was used to record FEV1 and peak expiratory flow (PEF). The handheld spirometers included an electronic patient diary function to collect asthma symptom scores, rescue medication use, and study drug use. Patients performed spirometry on the handheld device at the investigational site prior to entering run-in. Patients were randomized 1:1:1:1 to Fp 30 mcg, Fp 55 mcg, FS 55/14 mcg or placebo, one inhalation twice daily. During the 12-week treatment period, patients recorded their asthma symptom scores and rescue SABA use twice daily at approximately the same times of the day. After this, they performed lung function assessments of FEV1 and PEF. Following lung function assessments, patients took one inhalation of their blinded study drug and recorded dosing in the patient diary component of the handheld device. Patients withheld dosing with short acting

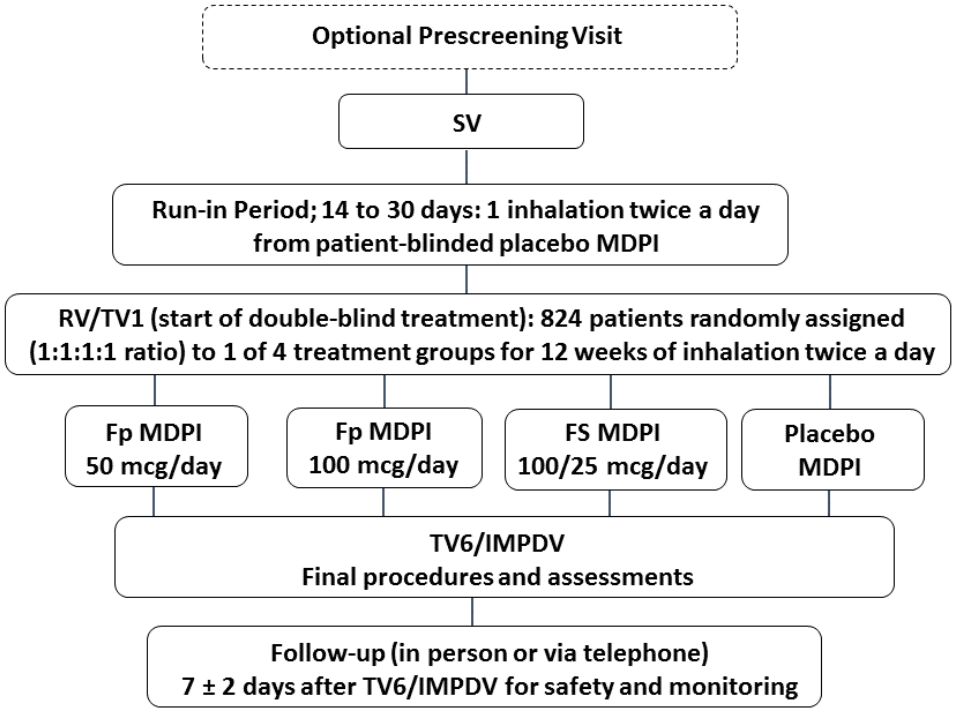
bronchodilator for four hours prior to lung function assessments at home. On the morning of the in-center trial visit, patients recorded symptoms and performed lung function assessments at home as usual but delayed drug dosing until arriving at the trial center. SABA use was withheld for six hours prior to lung function assessments. At the visits, instruction and training were provided and patients again performed lung function assessments at approximately 12 hours after their last dose of study drug. Patients then took their study drug and performed 1-hour post-dose FEV1 at the trial center. The highest value of FEV1 from 3 acceptable and 2 repeatable maneuvers was recorded. At trial visits, adverse events and clinical history were collected. The Childhood Asthma Control test (C-ACT) was completed prior to any other trial assessments by the patient and caregiver as applicable. On non-study visits weeks, telephone assessments were conducted as needed for safety or asthma-related issues. At the end of the trial, the safety follow up visit was conducted either in the trial center or via telephone at approximately 7 days after the last study visit at week-12.

During the trial, patients who met criteria for asthma worsening were assessed in the trial center, if possible, prior to changing medications. If the medical monitor and investigator assessed that study drug should be discontinued, then a discontinuation visit was conducted, and the patient remained in the trial for the purposes of study procedures aside from study drug dosing. Criteria were as follows:

- Morning FEV1 by handheld device measured at home fell below the FEV1 stability limit (defined as 80% of the highest acceptable FEV1 obtained prior to SABA) on 4 or more days (did not have to be consecutive) out of any 7-day period.
- The patient had experienced any of the following during any consecutive 7-day period:
    - 3 or more days in which 8 or more inhalations/day of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) were used (any 3 days in the consecutive 7-day period)
    - 3 or more days in which the patient experienced a nighttime asthma symptom score of more than 2 (any 3 days in the consecutive 7-day period)

The study schematic and assessment schedule are summarized in Figure 3 and 8.

Figure 3. Study Schema



Source: Applicant's Clinical Trial Report, page 32
Abbreviations: Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; IMPDV, investigational medicinal product discontinuation visit; MDPI, multidose dry powder inhaler; RV, randomization visit; SV, screening visit; TV, treatment visit
Fp MDPI 50 and 100 mcg/day nominal dose is equivalent to 30 and 55 mcg metered dose given BID, respectively
FS MDPI 100mcg/day nominal dose is equivalent to 55/14 mcg metered dose given BID

Table 8. Schedule of Assessments

Study Period	Placebo Run-In		Double-Blind Treatment Period (Visit Week)						Follow-Up
Visit Number	SV[a]	RV/TV1[b]	TV2	TV3	TV4	TV5	TV6	IMPDV	FV
Procedures and Assessments	Screening	Baseline	W1	W2	W4	W8	W12	IMPD	W13
Allowed Time Windows	-30 to -14 days	Day 1	Day 8 ±2 days	Day 15 ±2 days	Day 29 ±2 days	Day 57 ±2 days	Day 85 ±2 days	±2 days	Day 92 ±2 days
Informed consent/assent	X								
Medical history[c]	X								
Prior medication history	X								
Inclusion and exclusion criteria	X								
Demography	X								
Begin run-in	X								
Perform randomization and treatment assignment in IRT[b]		X							
Randomization criteria		X							
Adverse event inquiry and recording	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X
Vital signs measurement[d]	X	X	X	X	X	X	X	X	
Full physical examination, including weight and height	X						X	X	
Directed cardiopulmonary examination		X							
Oropharyngeal examination[e]	X	X	X	X	X	X	X	X	
Urine pregnancy test (female patients of childbearing potential)	X	X	X	X	X	X	X	X	
Perform lung function assessments (FEV1 and PEF) by handheld device with response to bronchodilator testing[f]	X								
Perform lung function assessments (FEV1 and PEF) by handheld device predose[g]	X	X	X	X	X	X	X (morning only)	X	
Perform lung function assessments (FEV1) by handheld device 1-hour post-dose at the investigational center[h]		X	X	X	X	X	X (morning only)	X	

Study Period	Placebo Run-In		Double-Blind Treatment Period (Visit Week)						Follow-Up
Visit Number	SV[a]	RV/TV1[b]	TV2	TV3	TV4	TV5	TV6	IMPDV	FV
Procedures and Assessments	Screening	Baseline	W1	W2	W4	W8	W12	IMPD	W13
Allowed Time Windows	-30 to -14 days	Day 1	Day 8 ±2 days	Day 15 ±2 days	Day 29 ±2 days	Day 57 ±2 days	Day 85 ±2 days	±2 days	Day 92 ±2 days
Conduct training for use of handheld device	X	X	X	X	X	X		X	
Asthma control questionnaire (C-ACT)		X			X	X	X	X	
Dispense/collect run-in IMP kit	X	X						X	
Conduct training for IMP administration and have patient demonstrate proper technique using the provided training inhaler[i]	X	X	X	X	X	X			
Observe patient dosing with IMP		X	X	X	X	X	X		
Dispense/collect rescue medication[j]	X	X	X	X	X	X	X		
Dispense/collect double-blind IMP kit		X		X	X	X	X	X	
Assess alert criteria for worsening asthma		X	X	X	X	X	X	X	
Distribute/collect handheld device[k]	X	X	X	X	X	X	X	X	
Discuss and record recommended asthma therapy[l]							X	X	
End IMP in IRT system							X	X	
End study participation in IRT system[m]							X	X	

Source: Trial 30003 CSR; table 2; page 33

[a] Patients attended a prescreening visit up to 15 days before the SV. The SV occurred up to 30 days prior to the RV. Patients who failed to meet baseline lung function assessments by handheld device requirements retested within 7 days of their initial SV. Patients who demonstrated a response to a bronchodilator by ≥10% and <14.50% entered the run-in period but underwent repeat lung function assessments and another bronchodilator test in 14±2 days and attempted lung function assessments and response to a bronchodilator within 14 more days if needed (as applicable). Patient-blinded drug was dispensed at each visit until the patient qualified for or failed randomization. Informed consent/assent was done at the SV unless it was already completed at a prescreening visit.

[b] The RV occurred up to 30 days following the SV. The patient's home FEV1 by handheld device was reviewed, and the average of the 5 highest daily values (3 attempts) for trough morning FEV1 out of the last 7 days prior to RV was 40% to 85% predicted for age, height, sex, and race (Quanjer et al 2012) with asthma symptom criteria, the C-ACT score was ≤19 to be elig ble for randomization. The patient met the lung function assessment requirements at the investigational center and all other study criteria. Elig ble patients were assigned a patient randomization identification number via the IRT system that was different than the one received at screening.

[c] The medical history was obtained by the investigator or designated study personnel. If there were no prior medical records available, the investigator documented the history of asthma, as reported by the patient, in the source document. Prior medical records were requested, or the reason if not requested was documented in the source documents. This was considered adequate history if it meets the inclusion criteria.

[d] Vital signs (BP and pulse rate) were obtained with the patient in a supine or semi erect/seated position after a 5-minute rest period.

[e] Oropharyngeal candidiasis at the RV excluded the patient from participating in the treatment period. Evidence of oropharyngeal candidiasis at any study TV or end of study TV was evaluated by obtaining a swab for culture. Patients who agreed to treatment continued to receive IMP. Treatment was not delayed for results of the culture.

[f] Lung function assessments (FEV1 and PEF) by handheld device and response to bronchodilator testing were conducted. Patients who were unable to perform lung function assessments were allowed to retest once within 7 days. Patients who met lung function assessment and response to bronchodilator requirements entered the run-in period. Patients who entered the run-in period with response to a bronchodilator ≥10% and <14.50% presented for repeat lung function assessments and another bronchodilator test within 14±2 days, during which they demonstrated at least a 15% response to a bronchodilator. Responses to bronchodilator of 14.50% to 14.99% were rounded to 15%. If the criteria were not met, patients continued in the run-in period for up to 14 additional days to meet the lung function assessment and response to a bronchodilator criterion (1 final attempt) for randomization. Patients who failed screening for inability to perform lung function assessments in a technically acceptable manner or due to FEV1 not meeting the inclusion criterion or demonstrated <10% response to a bronchodilator may retest once within 7 days of their initial SV provided that they have met all other inclusion criteria and none of the exclusion criteria at the SV. Patients who entered the run-in period with response to a bronchodilator ≥15% did not need to retest at the RV. For patients who needed to demonstrate the response to bronchodilator during the run-in, the RV was on another day.

[g] Daily morning and evening lung function assessments (FEV1 and PEF) by handheld device (after the patient was trained on its use and has demonstrated proper technique using the provided training device) were performed, except as indicated. The patient was instructed to perform 3 trough morning FEV1 maneuvers and 3 evening FEV1 maneuvers at home each day during participation in the run-in period and the treatment period (morning only on the final TV [TV6 (week 12)]). The highest FEV1 obtained at the SV was used to calculate the home FEV1 stability limit, which was used for review of alert criteria during the run-in period. The average FEV1 over 5 days prior to RV was used to calculate the alert criteria for the treatment period.

[h] 60-minute (±10 minutes) post-dose lung function assessments were performed at the investigational center at all visits (excluding patients placed on alternative therapy where the patient did not dose, but a 1-hour assessment was still collected).

[i] Except patients who had been placed on alternative therapy.

[j] Rescue medication was dispensed for all patients entering the run-in period. At each visit, the study personnel determined if the patient had adequate rescue medication remaining (based on current use) or dispensed a new albuterol/salbutamol HFA MDI. A second inhaler was provided for use at school or camp, as applicable. Rescue medication dispensed at SV was used for response to a bronchodilator test.

[k] The investigational center staff verified that the information from the patient diary built into the handheld device was up to date and identified any potential missing data or deviations upon review of the patient diary built into the handheld device at that visit. The device was collected and inspected to make sure it was not damaged and the data was downloaded at each clinic visit. Once inspected, the same handheld device was redispensed to the patient unless it needed to be replaced.

[l] The investigator discussed ongoing asthma treatment with the patient after lung function assessments were completed, and any medication started for the purpose of ongoing asthma treatment was not considered a protocol violation. This treatment, if instituted, was entered in the CRF as ongoing therapy.

[m] End of study participation in the IRT system took place at the last visit during the treatment period (i.e., at TV6 for patients who completed the treatment period, or at the IMPDV for patients who discontinued the study prematurely [patients who withdrew consent]).

Abbreviations: BP, blood pressure; C-ACT, Childhood Asthma Control Test; CRF, case report form; FEV1, forced expiratory volume in 1 second; FV, follow-up visit; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; IMP, investigational medicinal product; IMPD, investigational medicinal product discontinuation; IMPDV, investigational medicinal product discontinuation visit; IRT, Interactive Response Technology; PEF, peak expiratory flow; RV, randomization visit; SV, screening visit; TV, treatment visit; W, week

Study population

This study enrolled pediatric asthma patients age 4 to <12 years of age with a planned enrollment of approximately 200 patients per treatment arm.

Key inclusion criteria included:

- Male or female 4 to 11 years old, generally healthy besides asthma.
- Diagnosis of asthma as per NIH guidelines and present for ≥3 months before screening visit.
- Persistent asthma with FEV1 ≥50 % and ≤90% predicted for age, height, sex, and race (also called percent predicted FEV1, abbreviated as ppFEV1).
- Stable asthma therapy for 30 days prior. Permitted asthma therapies included ICS, ICS/LABA, and leukotriene receptor antagonists. Patients on SABA only were not eligible for the trial.
- The patient has demonstrated a greater than 10% response to a bronchodilator (2 to 4 inhalations of albuterol or salbutamol) from screening FEV1.
- Able to perform technically acceptable lung function assessments by handheld device.
- Able to use MDPI. Assistance by caregivers was permitted.
- Able to withhold SABA for 6 hours

Key exclusion criteria included:

- History of life-threatening asthma defined as intubation, hypercapnia, respiratory arrest, hypoxic seizures
- Asthma exacerbation requiring systemic corticosteroids or asthma hospitalization within 30 days prior to screening visit
- Initiation or planned escalation of immunotherapy. Patients on stable immunotherapy for 30 days or more, with initiation of immunotherapy prior to 90-days prior, were eligible for inclusion.
- Immunosuppressive medication use within 30 days of screening visit
- Suspected or proven bacterial or viral infection of the middle ear, sinus or respiratory tract that was unresolved at least 2 weeks prior to the screening visit
- Known medical history of other clinically significant diseases
- Pregnant or lactating
- Current or past smoker

Key Randomization Criteria (assessed after screening period at randomization visit)

- The average of the 5 highest values for trough morning FEV_1 obtained at home (by handheld device) out of the last 7 days prior to RV is within 40% to 85% predicted for age, height, sex, and race.
- The patient's C-ACT score at the randomization visit is ≤19.
- The patient has demonstrated at least a 15% response to a bronchodilator from baseline FEV_1 within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent at SV or during the run-in period as measured by handheld device.

- The patient has had no significant changes in asthma medications during run-in, excluding the albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent used as rescue medication or run-in placebo MDPI as supplied per protocol.
- The patient has not had a respiratory tract infection during the run-in period.
- The patient has had no asthma exacerbation during the run-in period, defined as any worsening of asthma requiring any significant treatment other than rescue albuterol/salbutamol HFA MDI or equivalent or the patient's run-in MDPI. This includes requiring the use of systemic corticosteroids, inhaled corticosteroids or other medications used to control asthma or are prohibited medications, and/or ER/urgent care clinic visit or hospitalization.
- The patient has not experienced an adverse event that would result in failure to continue to meet selection criteria.
- The patient has not used any of the prohibited concomitant medications during the run-in period

These criteria are generally reasonable and would result in the enrollment of persistent asthmatic patients who require maintenance medications.

Study Endpoints

Primary endpoints:
The co-primary efficacy endpoints were as follows:

- For FS MDPI 55/14 mcg versus Fp MDPI 55 mcg: the change from baseline in 1-hour post-dose percent predicted morning FEV1 at week 12. This was the first endpoint analyzed according to the statistical analysis plan.
- For Fp MDPI 55 mcg and 30 mcg versus placebo: the change from baseline in weekly average of the percent predicted trough morning FEV1 at week 12

Secondary endpoints:
The secondary efficacy endpoints were as follows:

- Change from baseline in the weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period
- Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12
- Change from baseline in the weekly average of the total daily asthma symptom score (defined as the average of the daytime and nighttime scores) over weeks 1 through 12
- Change from baseline in asthma control (measured by Childhood Asthma Control Test [C-ACT]) over the 12-week treatment period
- Time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use

- Proportion of patients who discontinued from study drug for asthma exacerbation during the 12-week treatment period (defined as in randomization criteria)

The C-ACT is a patient-completed tool used for the assessment of overall asthma control in childhood.[6] The first 4 items of the test are completed by the patient, while the last 3 items are completed by the patient's parents/legal guardians/caregivers. Lower scores indicate worse asthma control. A cutoff score of 19 indicates patients with poorly controlled asthma.

Exploratory endpoints:
The exploratory efficacy endpoints were as follows:

- Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12
- Change from baseline in the percentage of rescue-free days (defined as 24-hour periods with no rescue medication usage) during the 12-week treatment period
- Change from baseline in the percentage of symptom-free days (defined as 24-hour periods with asthma symptom score of 0) during the 12-week treatment period
- Change from baseline in the percentage of asthma-control days (defined as 24-hour periods with asthma symptom score of 0 and no rescue medication usage) during the 12-week treatment period
- Change from baseline in 1-hour post-dose percent predicted morning FEV1 at week 1
- Change from baseline in the weekly average of daily evening PEF over the 12-week treatment period
- Change from baseline in the weekly average of the percent predicted trough morning FEV1 at weeks 1, 2, 4, and 8
- Proportion of patients who achieve at least a 15% increase in morning FEV1 at 1-hour post dose at day 1 (randomization visit /treatment visit 1), week 1, and week 12
- Change from baseline in asthma control (measured by C-ACT) score at weeks 4, 8,and 12
- Time to consistent onset of effect defined as the decrease from baseline in daily rescue medication use on 3 consecutive days

Safety endpoints:
The safety endpoints were as follows:

- Incidence of adverse events throughout the study
- Vital signs assessments throughout the study
- Oropharyngeal examination findings at each visit
- Physical examination findings at baseline and at week 12 or at the study drug discontinuation visit

[6] Liu A *et al.* Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007; 119: 817–825

Statistical Analysis Plan

The statistical analysis plan was prespecified prior to unblinding. All efficacy analyses were conducted on the intention-to-treat (ITT) analysis set. The ITT analysis set includes all randomized patients.

The safety analysis set includes all randomized patients who receive at least 1 dose of study treatment. In the safety analysis set, treatment was assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified. The safety analysis set was used for all analyses of safety data.

The estimands selected for the 2 primary endpoints assessed the change from baseline due to the initially randomized treatment as actually taken. These estimands assess the effectiveness at week 12, focusing on the causal effects attributable to the initially randomized medication.

For patients discontinue study treatment, the applicant stated that they will encourage the patient to continue in the study and return for planned visits until the study completion in order to collect data after IMP discontinuation. However, these collected data was not included in the primary efficacy analyses.

The applicant argued following reasons why they do not include the data collected after discontinuation of study treatment in the primary efficacy analyses:

After a patient discontinues study treatment due to worsening asthma, the patient will be placed on alternative asthma therapies. The first choice will be ICS or a combination of ICS/LABA, exactly the classes of drugs being studied. Improvement of asthma would be expected as rapidly and early as 1 week for FEV1 for placebo patients placed on ICS. It has also been shown that patients placed on ICS with long acting beta-agonists can have significant improvement in serial FEV1 measurements on the same day. Therefore, any patient who discontinued IMP and was placed on alternative therapies would be expected to have rapid and demonstrable improvements in lung function. It is expected that patients randomized to placebo would discontinue IMP due to worsening asthma at a higher rate than those randomized to active treatment. The inclusion of patients who failed therapy and who were then treated with alternative medication would blunt the treatment effect, potentially causing the study to fail due to the analysis rather than the effectiveness of the treatment given during the study. These patients no longer represent a true placebo population and including them in the population for the primary outcome is not consistent with treatment by placebo. As a matter of fact, if retrieved drop outs placed on the alternative therapy such as ICS or ICS/LABA treatments, the efficacy would be compared between two identical classes of drugs, making such comparison not appropriate for the clinical trial designed and powered as the placebo-controlled trial.

<u>Sample Size Determination</u>

Sample size and power calculations were driven by demonstrating superiority of FS MDPI 50/12.5 mcg BID over Fp MDPI 50 mcg BID in change from baseline in 1-hour post-dose morning ppFEV1 at week 12 and the superiority of Fp MDPI 50 mcg BID over placebo in change from baseline in trough morning ppFEV1 at week 12.

The analysis of variance (ANOVA) model with only a single factor of treatment group was used to demonstrate the superiority comparison of FS MDPI 50/12.5 mcg BID versus Fp MDPI 50 mcg BID, following assumptions were made:

- Assume common SD of 22%, overall mean change from baseline of 6.5%
- Power of 80% at a 2-sided significance level of 5%

With these assumptions, 181 patients per treatment group were required for the test of FS MDPI 50/12.5 mcg BID and Fp MDPI 50 mcg BID.

The ANOVA model with only a single factor of treatment group was used to demonstrate the superiority comparison of Fp MDPI 50 mcg BID versus placebo, following assumptions were made:

- Assume common SD of 17%, overall mean change from baseline of 5%
- Power of 80% at a 2-sided significance level of 5%

With these assumptions, 181 patients per treatment group were required for the test of Fp MDPI 50 mcg BID versus placebo.

Assuming a dropout rate of 12%, a total of 824 patients (206 patients per treatment group) were randomized. These assumptions were revised assumptions based on an unplanned blinded data quality evaluation. The final sample size was based on the reassessment on the revised assumptions.

Statistical Methods

The co-primary endpoint of change from baseline in 1-hour post-dose morning ppFEV1 at week 12 was analyzed using an ANCOVA model with effects due to baseline trough morning ppFEV1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS (non-corticosteroid)), and study drug treatment group. The estimated treatment difference between FS and Fp was presented together with the 2-sided 95% CI for the difference and the p-value.

The second co-primary endpoint of change from baseline in weekly average of morning ppFEV1 at week 12 was analyzed using an ANCOVA model with the same effects as the first co-primary variable. The estimated treatment difference between FP and the placebo group was presented together with the 2-sided 95% CI for the difference and the p-value.

In the analyses of both co-primary endpoints, missing data that are caused by early dropouts from the study (regardless of availability of retrieved dropout data) were imputed using reference-based multiple imputations which represents a missing not at random (MNAR) mechanism. The reference-based multiple imputation method multiply imputes the missing

data in treatment group based on an imputation model built using data from the placebo group.

The change from baseline in the weekly average of daily morning (predose and prerescue bronchodilator) PEF over the 12-week treatment period was analyzed using an MMRM with effects due to baseline weekly average of daily morning PEF, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction.

The change from baseline in the weekly average of total daily (24-hour) use of albuterol/ salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12, the change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 through 12, and the change from baseline in C-ACT score over the 12-week treatment period were analyzed using an MMRM similar to the endpoint of daily morning PEF.

The time to first onset of effect, defined as the number of days elapsed from the date of randomization to the first date of decrease from baseline in daily rescue medication use was analyzed using a log-rank test to compare the survival curves. Time to first onset of effect was displayed graphically with a Kaplan-Meier figure, and median time to first onset of effect and associated 95% CIs were provided.

The proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period was analyzed using a logistic regression model with effects due to previous therapy (ICS or NCS) and treatment.

Multiplicity Control

For the analysis of the co-primary endpoints, a fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the 0.05 level. The testing procedures are listed in Table 9.

Table 9. Multiple Testing Procedures

Sequence	Primary Endpoint	Hypothesis Testing
1	**[1]** Change from baseline in1-hour postdose percent predicted morning FEV_1 at week 12	FS MDPI 50/12.5 mcg BID vs. Fp MDPI 50 mcg BID
		↓
2	**[2]** Change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12	Fp MDPI 50 mcg BID vs. Placebo
		↓
3	**[2]** Change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12	Fp MDPI 25 mcg BID vs. Placebo

Source: Excerpted from Applicant's SAP Table 7, Page 43.
Nominal doses are used; nominal doses of Fp 25 mcg, Fp 55 mcg, and FS 55/14 mcg correspond to the metered doses of Fp 30 mcg, Fp 55 mcg, and FS 55/14 mcg).
Abbreviations: BID, twice daily; FEV_1, forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler

If the p-value is less than 0.05 for the 3 inferential comparisons in the primary analysis, inferential testing will be extended to the secondary analysis.

Testing of secondary efficacy variables for the study drugs was performed in the sequential manner described in Table 10 (Fp MDPI) and Table 11 (FS MDPI).

Treatment comparisons will begin with the change from baseline in weekly average of daily trough morning PEF (first secondary endpoint) with Fp MDPI 55 mcg versus placebo for Fp MDPI, or FS MDPI 55/14 mcg versus placebo for FS MDPI. If the resulting p-value is less than 0.05, the next comparison(s) of interest will be made according to the direction of the arrows.

This procedure allows for control of the Type I error for comparisons at a particular study drug/strength over the 6 secondary endpoints, as well as comparisons over study drugs/strengths within a particular endpoint. However, it does not control the overall Type I error, nominal p-value will be reported.

In summary, multiplicity was not strongly controlled among all the secondary endpoints. There were no appropriate alpha splits for multiple outgoing tests. All p-values for hypothesis testing were compared to 0.05. If the p-value was less than 0.05 and all tests in a higher order were less than 0.05, then the claim is nominally significant.

Table 10. Sequence of Testing Secondary Endpoints for Fp MDPI

Secondary Endpoint	Hypothesis Testing	
	Fp MDPI 50 mcg vs. Placebo	**Fp MDPI 25 mcg vs. Placebo**
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓
[B] Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutomol inhalation aerosol (number of inhalations) over weeks 1 through 12	↓ →	↓
[C] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 through 12	↓ →	↓
[D] Change from baseline in asthma control (measured by C-ACT) score over the 12-week treatment period	↓ →	↓
[E] Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use	↓ →	↓
[F] Proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period	→	

Source: Excerpted from Applicant's SAP Table 8, Page 44.
Nominal doses are used; nominal doses of Fp 25 mcg, Fp 55 mcg, and FS 55/14 mcg correspond to the metered doses of Fp 30 mcg, Fp 55 mcg, and FS 55/14 mcg).
Abbreviations: C-ACT, Childhood Asthma Control Test; Fp, fluticasone propionate; IMP, investigational medicinal product; MDPI, multidose dry powder inhaler; PEF, peak expiratory flow

Table 11. Sequence of Testing Secondary Endpoints for FS MDPI

Secondary Endpoint	Hypothesis Testing		
	FS MDPI 50/12.5 mcg vs. Placebo	FS MDPI 50/12.5 mcg vs. Fp MDPI 25 mcg	FS MDPI 50/12.5 mcg vs. Fp MDPI 50 mcg
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓ →	↓
[B] Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutomol inhalation aerosol (number of inhalations) over weeks 1 through 12	↓ →	↓ →	↓
[C] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 through 12	↓ →	↓ →	↓
[D] Change from baseline in asthma control (measured by C-ACT) score over the 12-week treatment period	↓ →	↓ →	↓
[E] Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use	↓ →	↓ →	↓
[F] Proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period	→	→	

Source: Excerpted from Applicant's SAP Table 9, Page 45.
Nominal doses are used; nominal doses of Fp 25 mcg, Fp 55 mcg, and FS 55/14 mcg correspond to the metered doses of Fp 30 mcg, Fp 55 mcg, and FS 55/14 mcg).
Abbreviations: C-ACT, Childhood Asthma Control Test; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; IMP, investigational medicinal product; MDPI, multidose dry powder inhaler; PEF, peak expiratory flow

Sensitivity Analysis

To evaluate alternative estimands and assess the robustness of the primary efficacy results, following sensitivity analyses were proposed in the SAP for the 2 primary efficacy endpoints:

- Effectiveness with retrieve dropout data
- Treatment completer analysis
- Tipping point analysis with multiple imputations
- 2-dimensional tipping point analysis with multiple imputations
- Mixed approach of LOCF and baseline observation carried forward (BOCF)
- MMRM

Sub-Group Analyses

The following subgroup analyses were proposed for the primary efficacy endpoints:

- By sex (male and female)
- By age group (4-8 and 9-11 years)

- By race (white, black, and other)
- By region (US and non-US)
- By previous therapy (ICS and NCS)

The subgroup analysis used the same analysis model as the full data analyses but a subset of the full dataset.

Protocol Amendments

The protocol was amended once. The original protocol date was September 13, 2016. The protocol was amended on June 5, 2018. The major change in this amendment was an increase in sample size from 600 to 824 patients. The protocol was amended after routine blinded data monitoring of Trial 30003 revealed that the standard deviation for the overall study population was higher than the initial assumptions. FEV1 stability monitoring revealed that several participants had poor FEV1 due to poor effort rather than worsening asthma. This was attributed to the patients' young age and inability to coordinate effort. To ensure quality FEV1 data and the integrity of the study, Teva performed an unplanned blinded data quality evaluation and sample size reassessment. Based on the observed blinded 410 completed patients, the initial assumptions for standard deviation, power calculation and sample size were revised.

8.1.2. Study Results

Compliance with Good Clinical Practices

Trial 30003 was conducted in accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6. A statement of compliance with Good Clinical Practices is located in the clinical trial report.

Financial Disclosure

See Section 15.2.

Patient Disposition

Out of 1767 patients screened, a total of 841 patients were randomized in Trial 30003. Of the 841 patients who were randomized (intention-to-treat analysis set), 839 patients received at least 1 dose of study drug (safety analysis set). A total of 65 (8%) patients did not complete treatment. The most frequent reason for not completing treatment was lack of efficacy, which occurred in 33 (4%) patients. A total of 25 (3%) patients did not complete the study. The most frequent reason for not completing the study was withdrawal by parent/guardian, which occurred in 13 (2%) patients. The highest overall rate of withdrawal was observed in the placebo group (25 patients, 12%). Patient disposition for Trial 30003 is shown in Table 12.

Table 12. Patient Disposition (All Randomized Patients)

		Fp MDPI		FS MDPI	
Analysis Group, n (%)	**Placebo**	**30 mcg BID**	**55 mcg BID**	**55/14 mcg BID**	**Total**
Randomized	209 (100)	211 (100)	210 (100)	211 (100)	841 (100)
ITT analysis set	209 (100)	211 (100)	210 (100)	211 (100)	841 (100)
ITT did not receive study drug	0	0	2 (<1)	0	2 (<1)
ITT completer	184 (88)	197 (93)	196 (93)	199 (94)	776 (92)
ITT IMPD with retrieved data	20 (10)	11 (5)	7 (3)	9 (4)	47 (6)
ITT IMPD without retrieved data	5 (2)	3 (1)	5 (2)	3 (1)	16 (2)
Safety analysis set	209 (100)	211 (100)	208 (>99)	211 (100)	839 (>99)
PP analysis set	184 (88)	187 (89)	187 (89)	192 (91)	750 (89)
Completed treatment	184 (88)	197 (93)	196 (93)	199 (94)	776 (92)
Did not complete treatment	25 (12)	14 (7)	14 (7)	12 (6)	65 (8)
Adverse event	0	3 (1)	2 (<1)	2 (<1)	7 (<1)
Withdrawal by subject	1 (<1)	0	1 (<1)	0	2 (<1)
Withdrawal by parent/guardian	5 (2)	2 (<1)	3 (1)	2 (<1)	12 (1)
Noncompliance with study drug	2 (<1)	1 (<1)	0	2 (<1)	5 (<1)
Lost to follow-up	0	0	1 (<1)	2 (<1)	3 (<1)
Lack of efficacy	17 (8)	7 (3)	5 (2)	4 (2)	33 (4)
Other	0	1 (<1)	0	0	1 (<1)
Missing reason	0	0	2 (<1)	0	2 (<1)
Completed study	202 (97)	206 (98)	203 (97)	205 (97)	816 (97)
Did not complete study	7 (3)	5 (2)	7 (3)	6 (3)	25 (3)
Withdrawal by subject	0	0	1 (<1)	0	1 (<1)
Withdrawal by parent/guardian	6 (3)	3 (1)	3 (1)	1 (<1)	13 (2)
Protocol violation	0	1 (<1)	0	0	1 (<1)
Lost to follow-up	0	0	1 (<1)	3 (1)	4 (1)
Other	1 (<1)	1 (<1)	2 (<1)	2 (<1)	6 (<1)

Source: Statistical Reviewer
Abbreviations: BID, twice daily; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; IMPD, investigational medicinal product discontinuation; ITT, intent-to-treat; MDPI, multidose dry powder inhaler; n, number with indicated disposition; PP, per protocol

Protocol Violations/Deviations

A total of 162 (19%) patients had at least one protocol violation. Of the 162 patients, 39 (5%) did not have secondary efficacy parameters assessed as per protocol, 38 (5%) did not meet inclusion criteria, 35 (4%) took a prohibited concomitant medication, 13 (2%) did not meet Good Clinical Practice guidelines, and 21 (2%) did not meet randomization criteria. All other reasons were reported for 1% or less of all patients. There were slightly more protocol violations amongst the placebo group and FP MDPI 30 mcg group (other reasons) compared to other treatment groups. However, differences were generally small and unlikely to impact analyses. Protocol violations are summarized in Table 13.

Table 13. Protocol Violations by Treatment Group (ITT Analysis Set)

Violation Classification, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)	Total (N=841)
Patients with at least 1 important violation	46 (22)	46 (22)	35 (17)	35 (17)	162 (19)
Inclusion criteria	8 (4)	11 (5)	7 (3)	12 (6)	38 (5)
Randomization criteria	6 (3)	6 (3)	5 (2)	4 (2)	21 (2)
Study drug	2 (<1)	1 (<1)	0	4 (2)	7 (<1)
Randomization visit 1st dose run	3 (1)	4 (2)	2 (<1)	3 (1)	12 (1)
GCP guidelines	4 (2)	4 (2)	3 (1)	2 (<1)	13 (2)
Visit window	0	0	0	3 (1)	3 (<1)
Prohibited concomitant medication	13 (6)	9 (4)	6 (3)	7 (3)	35 (4)
Primary objective lung function assessments not obtained	5 (2)	0	1 (<1)	0	6 (<1)
Critical misuse of AM3 (handheld spirometer)	6 (3)	2 (<1)	3 (1)	0	11 (1)
Secondary objective lung function assessments not obtained	6 (3)	15 (7)	13 (6)	5 (2)	39 (5)
AM3 handheld spirometer compliance per visit	1 (<1)	0	0	0	1 (<1)
Other	0	2 (<1)	0	0	2 (<1)

Source: Applicant's Clinical Trial Report, Table 12, page 100. Verified by reviewer.
A patient may have met more than 1 criterion.
Abbreviations: AM3, asthma monitor 3; BID, twice daily; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; GCP, Good Clinical Practice; ITT, intent-to-treat; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with indicated specification

Demographic Characteristics

Selected demographic features for all randomized patients (ITT population) are shown in Table 14. In Trial 30003, patient demographics and baseline characteristics were generally balanced amongst the treatment groups. The majority of patients were male (61%), of white race (81%), and non-Hispanic or Latino ethnicity (76%). The mean age was 8.5 years with 45% of patients in the 4-to-8-year-old group and 55% of patients in the 9 to 11-year-old group.

Table 14. Demographics (ITT Analysis Set)

Demographic Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)	Total (N=841)
Sex, n (%)					
Female	79 38	74 35	80 38	91 43	324 39
Male	130 62)	137 65)	130 62)	120 57)	517 61)

Demographic Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)	Total (N=841)
Race, n (%)					
American Indian or Alaska native	0	1 0	2 1	0	3 0
Asian	1 0	0	2 1	3 1	6 1
Black or African American	33 16)	41 19)	32 15)	29 14)	135 16)
Native Hawaiian or other Pacific islander	1 0	0	0	0	1 0
Other	2 1	1 0	3 1	7 3	13 2
White	172 82)	168 80)	171 81)	172 82)	683 81)
Ethnicity, n (%)					
Hispanic or latino	47 22	0	55 26	45 22	51 24
Not Hispanic or latino	163 77	2 100	156 74	162 78	158 76
Not reported	1 1	0	0	1 1	0
Age group, n (%)					
4 to 8 years	93 44	92 44	98 47	93 44	376 45
9 to 11 years	116 56)	119 56)	112 53)	118 56)	465 55)
Age, years					
n	209	211	210	211	841
Mean	8.5	8.7	8.5	8.4	8.5
SD	1.98	1.83	1.94	2.05	1.95
Median	9.0	9.0	9.0	9.0	9.0
Minimum, maximum	4.0, 11.0	4.0, 11.0	4.0, 11.0	4.0, 11.0	4.0, 11.0
Region, n (%)					
Non-United States	84 40)	77 36)	93 44)	94 45)	348 41)
United States	125 60	134 64	117 56	117 55	493 59

Source: Medical reviewer, generated using OCS Analysis Studio, Custom Table Tool. For age in years, the source is the Applicant's Clinical Trial Report, Table 6, page 89

Abbreviations: BID, twice daily; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; ITT, intent-to-treat, MDPI, multidose dry powder inhaler; N, number of subjects in study arm; n, number of subjects with indicated demographic; SD, standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics such as height and weight, and asthma duration history were generally similar between treatment arms (Table 15). Prior medication use was also similar between treatment and consistent with an asthma population (not shown).

Table 15. Baseline Characteristics by Treatment Group (ITT Analysis Set)

Demographic Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)	Total (N=841)
Weight, kg					
n	209	211	210	211	841
Mean	34.4	35.9	34.7	35.4	35.1
SD	12.60	12.18	12.76	13.67	12.80
Median	31.9	33.0	32.0	32.2	32.2
Minimum, maximum	16.2, 96.6	19.6, 82.4	14.0, 79.9	15.0, 85.3	14.0, 96.6

Demographic Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)	Total (N=841)
Height, cm					
n	209	211	210	211	841
Mean	135.8	137.4	136.0	135.1	136.1
SD	12.80	12.37	13.03	13.65	12.97
Median	136.0	138.0	137.1	135.0	136.4
Minimum, maximum	104.0, 163.0	107.0, 172.7	99.0, 170.2	96.0, 167.0	96.0, 172.7
BMI, kg/m^2					
n	209	211	210	211	841
Mean	18.1	18.6	18.2	18.8	18.4
SD	4.02	3.86	4.29	4.56	4.19
Median	17.2	17.5	17.1	17.4	17.3
Minimum, maximum	10.9, 39.2	12.5, 34.9	11.8, 33.8	11.7, 34.2	10.9, 39.2
Duration of asthma, n (%)					
<3 months	0	0	0	0	0
3 to <6 months	9 (4)	12 (6)	8 (4)	11 (5)	40 (5)
6 months to <1 year	11 (5)	14 (7)	22 (10)	17 (8)	64 (8)
1 to <5 years	97 (46)	84 (40)	92 (44)	87 (41)	360 (43)
5 to <10 years	84 (40)	92 (44)	77 (37)	87 (41)	340 (40)
10 to <15 years	8 (4)	9 (4)	11 (5)	9 (4)	37 (4)
>15 years	0	0	0	0	0

Source: Applicant Clinical Trial Report, Table 6 and 9, page 90 and 95. Verified by reviewer.
Abbreviations: BID, twice daily; BMI, body mass index; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; ITT, intent-to-treat; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with indicated demographic; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was determined by the dose counter as well as the patient's electronic diary. In terms of compliance, 92% of patients were at least >80% compliant across treatment arms. Concomitant medication use was generally balanced between arms, with more cough and cold preparations and antihistamines used in the placebo arm as compared to active treatment arms. The FP 55 mcg treatment arm had more use of intranasal fluticasone propionate. Rescue med use of a short-acting beta-agonist was evaluated as a secondary endpoint and is discussed below. Overall use of systemic corticosteroids was low, in not more than 2% of patients in each arm.

Efficacy Results – Primary Endpoint

In Trial 30003, there were two co-primary endpoints. In order of testing hierarchy, these endpoints were as follows:

1. For FS versus Fp: the change from baseline in 1-hour post-dose morning ppFEV1 at week 12
2. For Fp versus placebo: the change from baseline in weekly average of the trough morning ppFEV1 (tFEV1) at week 12

For the first co-primary endpoint, change from baseline in 1-hour post-dose morning ppFEV1 at week 12, FS 55/14 mcg did not demonstrate statistically significant difference from FP 55 mcg

[difference versus FS 55 mcg (b) (4)]. For the second co-primary endpoint, the change from baseline in weekly average of the tFEV1 at week 12, the FP 55 mcg versus placebo treatment difference was (b) (4) with a 95% CI excluding null. However, given failure at the first co-primary endpoint, results for the second co-primary endpoint were not considered statistically significant. The difference in change from baseline in weekly average of tFEV1 of Fp 30mcg and placebo was (b) (4) with a 95% CI excluding null. The co-primary results are summarized in Table 16.

Table 16. Co-Primary Endpoint Results (ITT Analysis Set)

Primary Endpoint	Comparison	Estimate of Effect
[1] Change from baseline in 1-hour post-dose morning ppFEV1 at week 12	FS 55/14 mcg versus Fp 55 mcg	(b) (4)
[2] Change from baseline in weekly average of the trough morning ppFEV1 at week 12	Fp 55 mcg versus placebo	
[3] Change from baseline in weekly average of the trough morning ppFEV1 at week 12	Fp 30 mcg versus placebo	

Source: Statistical Reviewer
[a] Nominal p-value due to failure of enpoint(s) higher in the multiplicity hierarchy
Abbreviations: CI, confidence interval; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; ITT, intent-to-treat; PPEV1, percent predicted forced expiratory volume in 1 second

Additional comparisons between treatment arms for change from baseline in 1-hour post-dose ppFEV1 and weekly average tFEV1 are summarized in Table 17 and Table 18, respectively. For Fp 30mcg, Fp 50mcg, and FS 55/14mcg, for both change from baseline in 1-hour post-dose ppFEV1 and weekly average of tFEV1, results showed numerical improvements compared to placebo with 95% CIs excluding null.

Table 17. Change From Baseline in 1-Hour Post-Dose Percent Predicted Morning FEV1 at Week 12 by Treatment Group (ITT Analysis Set)

		Fp MDPI		FS MDPI
Variable	Placebo (N=209)	30 mcg BID (N=211)	55 mcg BID (N=210)	55/14 mcg BID (N=211)
Change in 1-hour post-dose percent predicted morning FEV1 (%) at week 12				(b) (4)
n	209	211	209	
LSM (SE)	8.9 (1.31)	16.8 (1.32)	16.4 (1.32)	
95% CI	(6.4, 11.5)	(14.2, 19.4)	(13.8, 19.0)	
Comparison to placebo				
Difference of LSM (95% CI)		7.9 (4.4, 11.3)	7.4 (4.0, 10.9)	
p-value		<0.001[a]	<0.001[a]	

Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)
Comparison to Fp 55 mcg BID				(b) (4)
Difference of LSM (95% CI)	--	--	--	
p-value	--	--	--	

Source: Statistical Reviewer
[a] Nominal p-value due to failure of enpoint(s) higher in the multiplicity hierarchy
[b] First co-primary endpoint
Abbreviations: BID, twice daily; CI, confidence interval; FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; LSM, least squares mean; MDPI, multidose dry powder inhaler; N, number of subjects in study arm; n, number of subjects with indicated change; SE, standard error

Table 18. Change From Baseline in Weekly Average of Percent Predicted Morning Trough FEV1 at Week 12 by Treatment Group (ITT Analysis Set)

Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=210)	FS MDPI 55/14 mcg BID (N=211)
Change from baseline in weekly average of the trough morning ppFEV1 at Week 12				(b) (4)
n	209	211	209	
LSM (SE)	7.3 (1.10)	13.3 (1.09)	14.2 (1.10)	
95% CI	(5.1, 9.4)	(11.1, 15.4)	(12.1, 16.4)	
Comparison to placebo				
Difference of LSM (95% CI)		6.0 (3.2, 8.8)	7.0 (4.1, 9.8)[b]	
p-value		<0.001[a]	<0.001[a]	
Comparison to Fp 55 mcg BID				
Difference of LSM (95% CI)	--	--	--	
p-value	--	--	--	

Source: Statistical Reviewer
[a] Nominal p-value due to failure of endpoint(s) higher in the multiplicity hierarchy
[b] Second co-primary endpoint
Abbreviations: BID, twice daily; CI, confidence interval; ppFEV1, percent predicted forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; LSM, least squares mean; MDPI, multidose dry powder inhaler; N, number of subjects in study arm; n, number of subjects with indicated change; SE, standard error

As the first co-primary endpoint failed to demonstrate that FS 55/14 mcg was superior to FP 55 mcg, the contribution of the salmeterol component to the FS 55/14 mcg has not been demonstrated. Therefore, these data do not provide support for the efficacy of FS 55/14 mcg, despite results for FS 55/14 mcg to placebo comparisons.

With regard to the Fp, both doses, results showed an improvement in weekly average of tFEV1 compared to placebo with 95% CIs excluding the null, with the higher dose being marginally higher. While these results cannot be considered statistically significant due to failure at the first co-primary endpoint, these FP data provide some support for the efficacy of Fp at both doses.

Data Quality and Integrity

There were no issues with data quality or integrity.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints included the following:

1. Change from baseline in the weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period
2. Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12
3. Change from baseline in the weekly average of the total daily asthma symptom score (defined as the average of the daytime and nighttime scores) over weeks 1 through 12
4. Change from baseline in asthma control (measured by Childhood Asthma Control Test [C-ACT]) over the 12-week treatment period
5. Time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use
6. Proportion of patients who discontinued from study drug for asthma exacerbation during the 12-week treatment period (defined as in randomization criteria)

Given failure at the first co-primary endpoint, results for all secondary endpoints were not considered statistically significant. Across all secondary efficacy endpoints, for the comparison FS 55/14 mcg versus Fp 55 mcg, the 95% CIs included null. With regard to FS 55/14 mcg versus placebo, numerical improvements were observed, and 95% CIs excluded the null. These results are consistent with the first co-primary endpoint. Results of the secondary endpoint analysis of FS 55/14 mcg versus FP 55 mcg are shown in Table 19. Note that results for time to onset of first effect (secondary endpoint #5) are not shown. Results for this endpoint for FS 55/14 mcg versus Fp 55 mcg and placebo had log-rank test p-values (b) (4) and (b) (4) respectively.

Table 19. Analyses Results of Secondary Endpoints for Fluticasone Propionate/Salmeterol Versus Fluticasone Propionate and Fluticasone Propionate/Salmeterol Versus Placebo (ITT Analysis Set)

	FS MDPI 55/14 mcg BID	
Endpoint	**FS Versus Placebo LSM (95% CI) p-value[a]**	**FS Versus Fp 55 LSM (95% CI) p-value[a]**
CFB in weekly average of daily trough morning PEF over 12-week: L/min	(b) (4)	
CFB in weekly average of total daily use of albuterol/ salbutamol inhalation aerosol over Weeks 1 through 12		
CFB in weekly average of total daily asthma symptom score over weeks 1 through 12		
CFB in asthma control (measured by C-ACT) over the 12-week treatment period		
Proportion of patients who discontinued from IMP for asthma exacerbation during the 12-week treatment period: odds ratio		

Source: Statistical Reviewer

[a] Nominal p-value due to failure of enpoint(s) higher in the multiplicity hierarchy

Abbreviations: BID, twice daily; C-ACT, childhood asthma control test; CFB, change from baseline; CI, confidence interval; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; IMP, investigational medicinal product; ITT, intent-to-treat; LSM, least squares mean; MDPI, multidose dry powder inhaler; PEF, peak expiratory flow

With regard to secondary endpoints results for Fp to placebo comparisons, results were generally consistent with the second co-primary endpoint. For the majority of secondary endpoints, results for both Fp doses demonstrated numerical improvements versus placebo with 95% CIs that excluded the null. The only secondary endpoints for which this was not the case was proportion of patients who discontinued study treatment due for asthma exacerbation for the Fp 55 mcg versus placebo comparison and time to onset of first effect for both doses. Results of the secondary endpoint analysis for Trial 30003 Fp 30 mcg and 55 mcg are shown in Table 20. Note that results for time to onset of first effect (secondary endpoint #5) are not shown. Results for this endpoint for Fp 55 mcg and Fp 30 mcg versus placebo had log-rank test p-values of 0.43 and 0.93, respectively.

Table 20. Analyses Results of Secondary Endpoints for Fluticasone Propionate Versus Placebo (ITT Analysis Set)

	Fp MDPI	
Endpoint	**55 mcg Versus Placebo LSM (95% CI) p-value[a]**	**30 mcg Versus Placebo LSM (95% CI) p-value[a]**
CFB in weekly average of daily trough morning PEF over 12-week: L/min	14.0 (7.0, 21.1) <0.001	16.6 (9.6, 23.7) <0.001
CFB in weekly average of total daily use of albuterol/ salbutamol inhalation aerosol over weeks 1 through 12	-0.3 (-0.4, -0.2) <0.001	-0.3 (-0.4, -0.1) <0.001
CFB in weekly average of total daily asthma symptom score over weeks 1 through 12	-0.1 (-0.2, -0.1) <0.001	-0.1 (-0.1, 0) 0.005
CFB in asthma control (measured by C-ACT) over the 12-week treatment period	1.0 (0.4, 1.5) <0.001	0.6 (0, 1.2) 0.035
Proportion of patients who discontinued from IMP for asthma exacerbation during the 12-week treatment period: odds ratio	0.365 (0.128, 1.044) 0.060	0.219 (0.062, 0.781) 0.019

Source: Statistical Reviewer
[a] Nominal p-value due to failure of enpoint(s) higher in the multiplicity hierarchy
Abbreviations: C-ACT, childhood asthma control test; CFB, change from baseline; CI, confidence interval; Fp, fluticasone propionate; IMP, investigational medicinal product; ITT, intent-to-treat; LSM, least squares mean; MDPI, multidose dry powder inhaler; PEF, peak expiratory flow

These secondary endpoint data, as with the co-primary endpoint data, suggest that while FS 55/14 may show numerical superiority to placebo, superiority to the Fp 55mcg is not supported as for all comparisons the 95% CI include the null. Therefore, as with the 1st co-primary endpoint, secondary endpoint data do not support the contribution of the salmeterol component to the combination.

With regard to Fp, secondary endpoint data are generally consistent with results from the 2nd co-primary endpoint. Both Fp doses demonstrated numerical superiority to placebo across the vast majority of secondary endpoints with 95% CIs excluding the null. While these results cannot be considered statistically significant due to failure at the first co-primary endpoint, these data are suggestive of efficacy for both Fp doses.

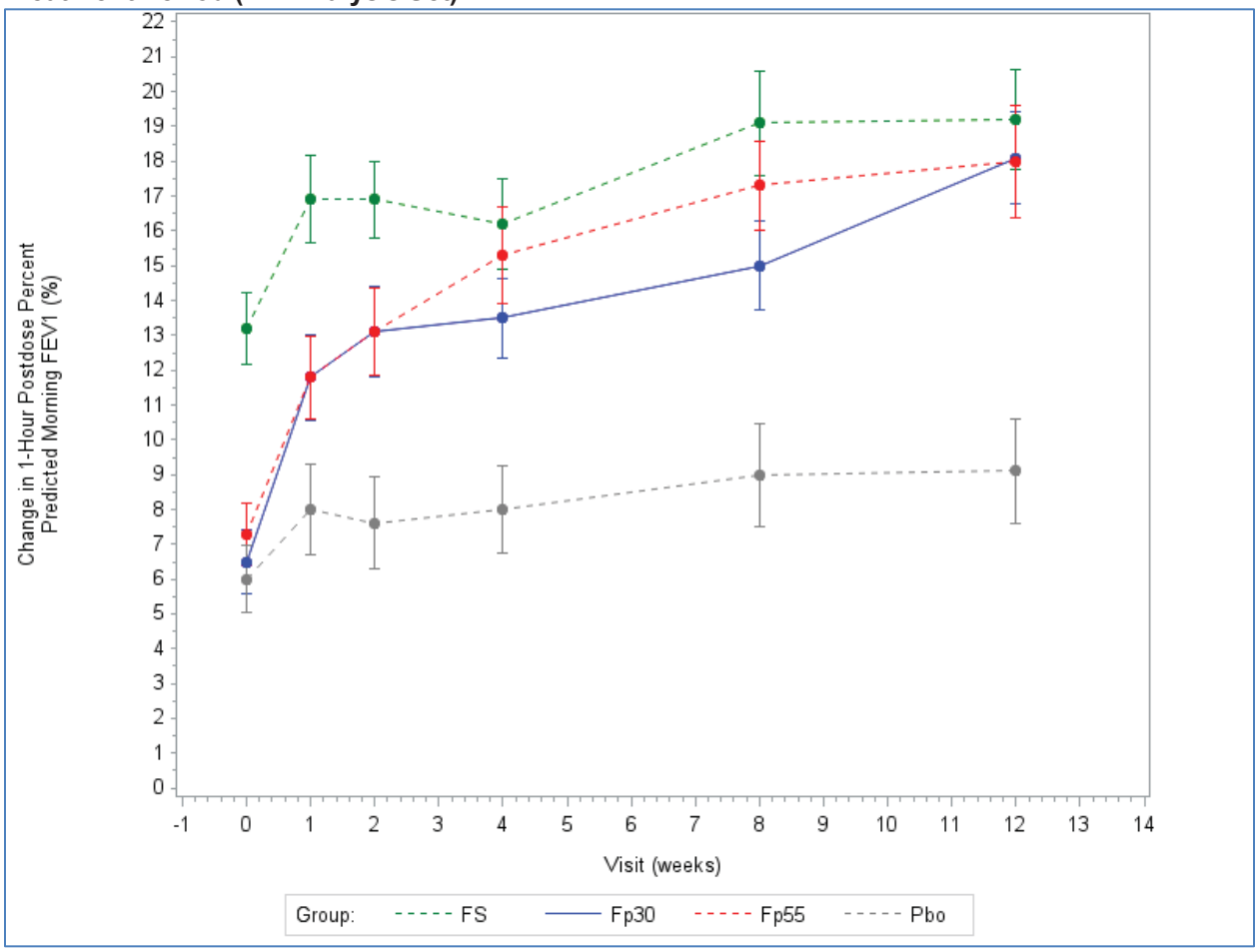
Dose/Dose Response

Trial 30003 evaluated two doses of Fp, 30 mcg and 55 mcg. For the co-primary endpoint relevant to Fp, the treatment effect for the higher dose was observed to be marginally numerically larger than for the lower dose. These data are consistent with the adult/adolescent program. In that program, the Fp 30 mcg showed a similar change in FEV1 from baseline to week 12, the primary endpoint, to the 55 mcg. Overall, these dose-response data do not clearly demonstrate that the Fp 55 mcg is superior Fp 30 mcg. However, as the safety of these two doses are largely similar and consistent with the known inhaled corticosteroid safety profile (see Section 8.2), either/both doses are reasonable choices. Moreover, given how asthma is clinically managed, the availability of two doses may be of benefit as it would allow for healthcare providers to 'step-up' therapy and may also facilitate transitioning patient from another ICS to Fp. With regard to FS, only one dose was explored in the trial 30003. For further details please refer to the clinical review of NDA 208798 and 208799 dated October 26, 2016.

Durability of Response

Trial 30003 was a 12-week treatment period with a 1-week safety follow-up. In general, the observed effect on both co-primary endpoints, qualitatively, did not appear to wane over time. Results are shown in Figure 4 and Figure 5.

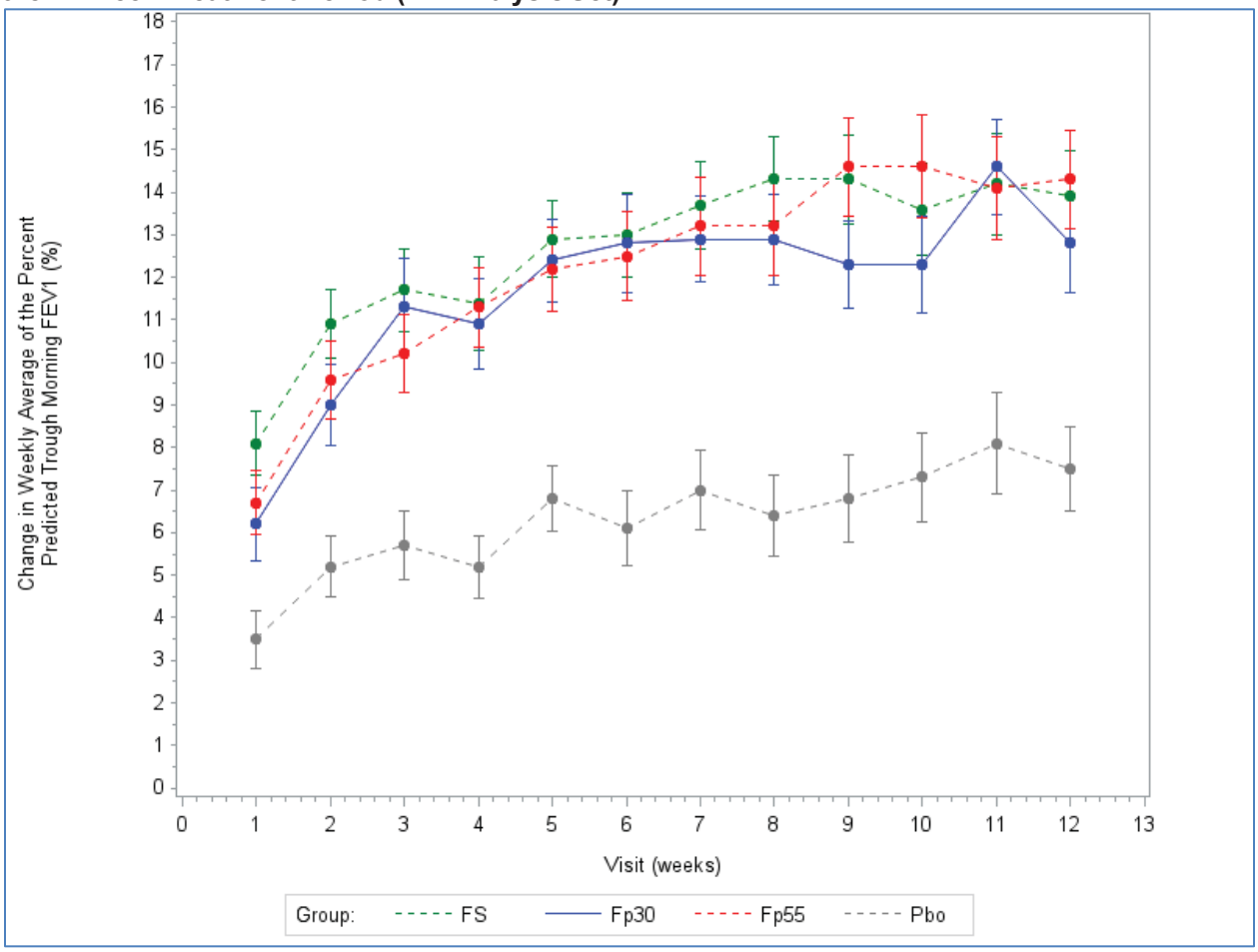
Figure 4. Change From Baseline in 1-Hour Post-Dose Percent Predict FEV1 Over the 12-Week Treatment Period (ITT Analysis Set)



Source: Statistical Reviewer

Abbreviations: FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; ITT, intent-to-treat; Pbo, placebo

Figure 5. Change From Baseline in Weekly Average of the Percent Predicted Trough FEV1 Over the 12-Week Treatment Period (ITT Analysis Set)



Source: Statistical Reviewer
Abbreviations: FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; ITT, intent-to-treat; Pbo, placebo

Persistence of Effect

Persistence of effect was not evaluated beyond the 12-week treatment period in Trial 30003. However, for FS 55/14 mcg, Fp 30 mcg, and Fp 55 mcg, effects would not be expected to persist following cessation of treatment as this class of product are not known to alter disease course.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

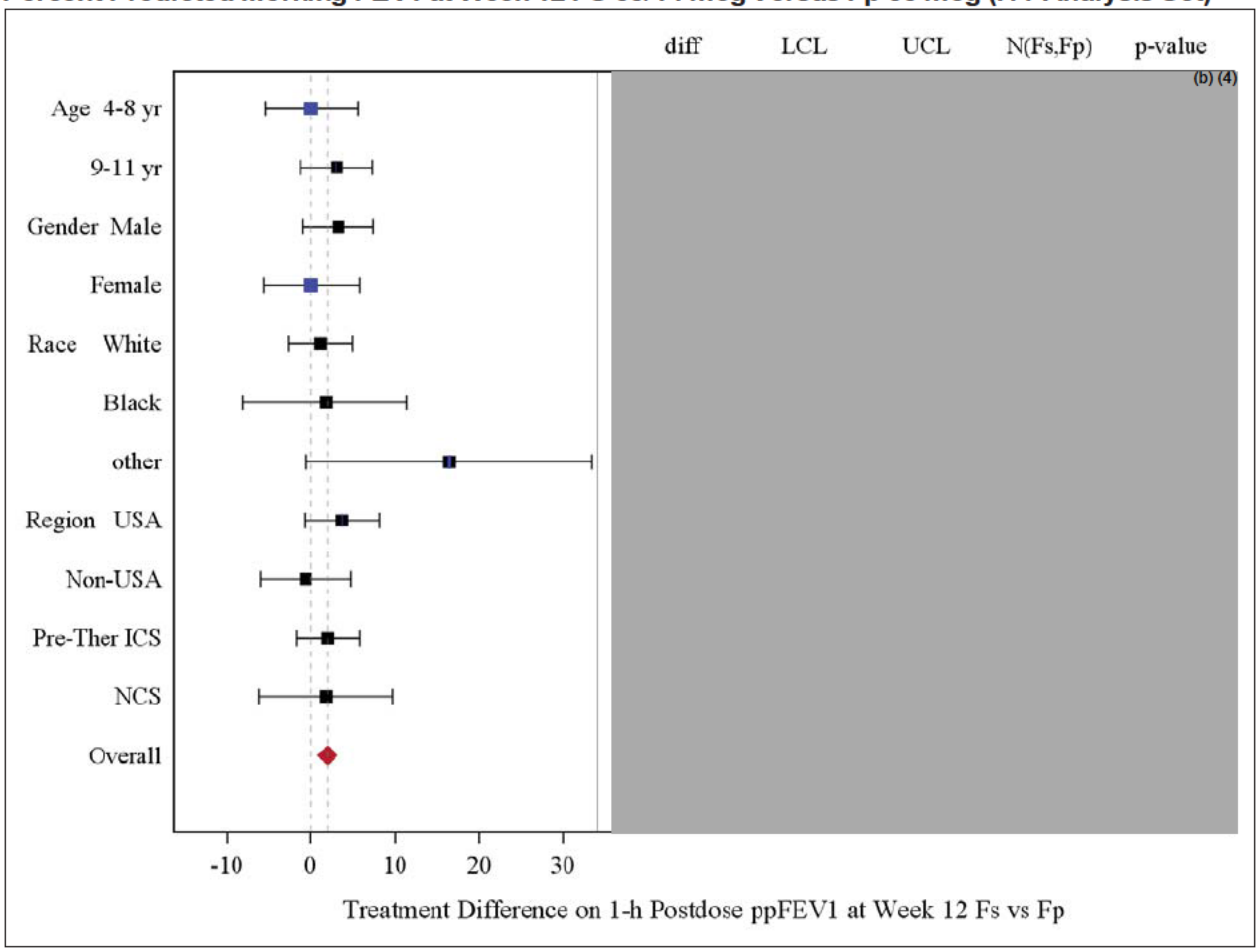
The Childhood Asthma Control test (C-ACT) was a patient reported outcome measure used in Trial 30003. The C-ACT is included in the discussion of secondary efficacy endpoints above.

Additional Analyses Conducted on the Individual Trial

For the primary endpoint, subgroup analyses were performed for the following factors: sex (male and female), age (4 to 8 year olds, and 9 to 11 year olds), race (White, Black and Other), region (US and non-US) and by previous therapy (ICS and non-corticosteroid).

Subgroup analyses on the first co-primary endpoint of 1-hour post-dose ppEFV1 at week 12 comparison of FS 55/14 mcg versus Fp 55 mcg is presented in Figure 6, comparison of Fp versus placebo is presented in Figure 7. These subgroup analyses results are consistent with the overall results. For the comparison of FS 55/14 mcg versus Fp 55 mcg, none of subgroup results p-value is less than (b) (4) which is consistent to the overall results p-value of 0.285.

Figure 6. Forest Plot of Co-Primary Endpoint of Change From Baseline in 1-Hour Post-Dose Percent Predicted Morning FEV1 at Week 12 FS 55/14 mcg Versus Fp 55 mcg (ITT Analysis Set)



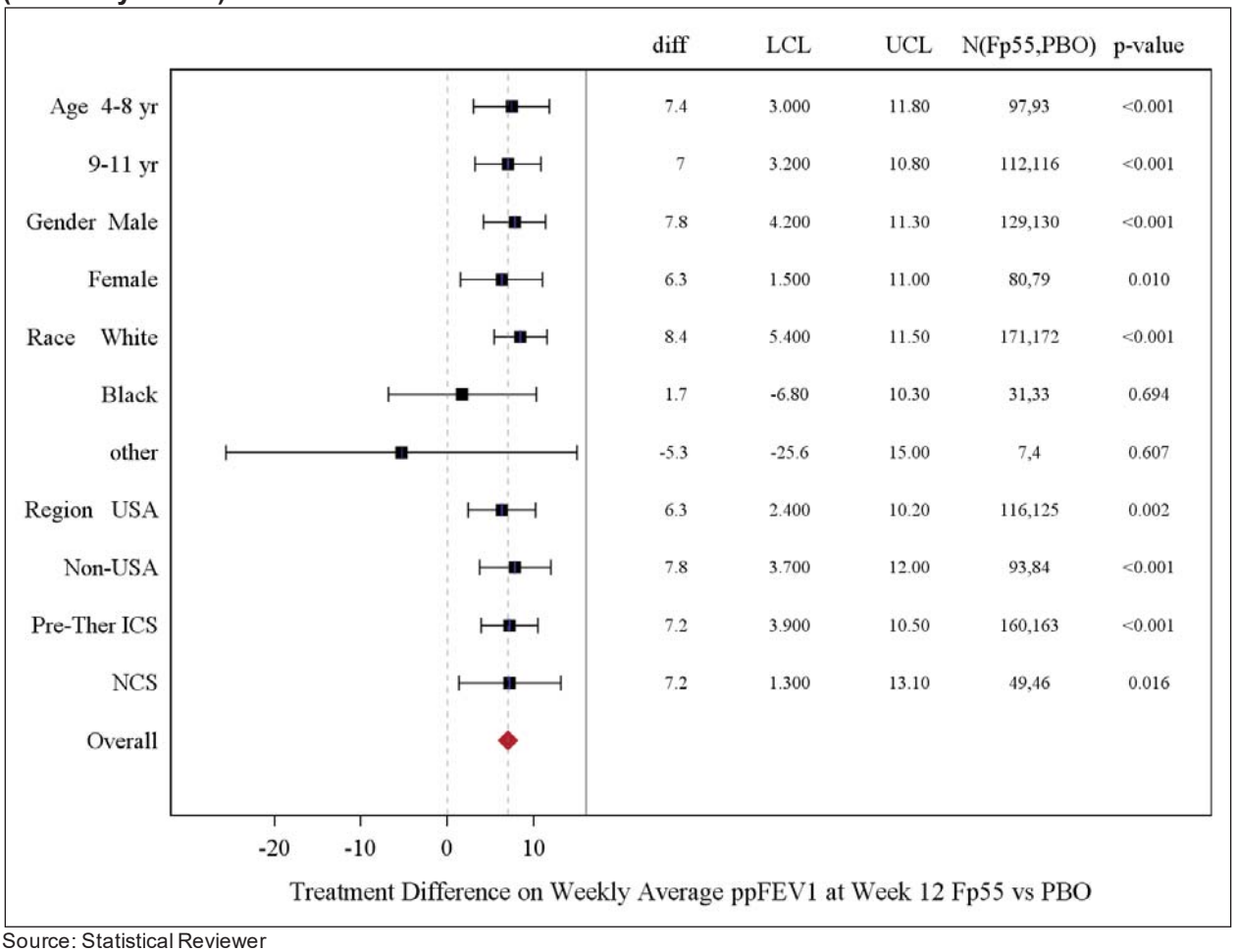
Source: Statistical Reviewer
Abbreviations: diff, difference; FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; h, hour; ICS, inhaled corticosteroid; ITT, intent-to-treat; LCL, lower control limit; N, number; NCS, no corticosteroid; ppFEV1, percent predicted forced expiratory volume in 1 second; Ther, therapy; UCL, upper control limit; USA, United States of America; yr, year

Subgroup analyses on the second co-primary endpoint of change from baseline in weekly average of ppFEV1 at week 12 comparison of Fp 55 mcg versus placebo is presented in Figure 7, comparison of Fp 30 mcg versus placebo is presented in Figure 8. These subgroup results are also consistent with the overall results. For comparison of Fp 55 mcg versus PBO, all subgroups results p-values are less than 0.05 except for the two subgroups of black and other race. Subgroup of other race has extremely small number of subjects in each arm. It is known that

extreme small number of subjects can cause results to be unstable. Subgroup of black race results p-value is greater than 0.05, but it trends consistent with the overall population. For comparison of Fp 30 mcg versus placebo comparison, all subgroups results demonstrated p-values are less than 0.05 except for other race, female, and no corticosteroid (NCS) subgroups. However, for subgroups of female and NCS, trends were consistent with the overall population. Other race has too few number of subjects to make definitive conclusions as their result is not stable.

In conclusion, for all the subgroups examined, subgroups analyses are generally consistent with the overall population.

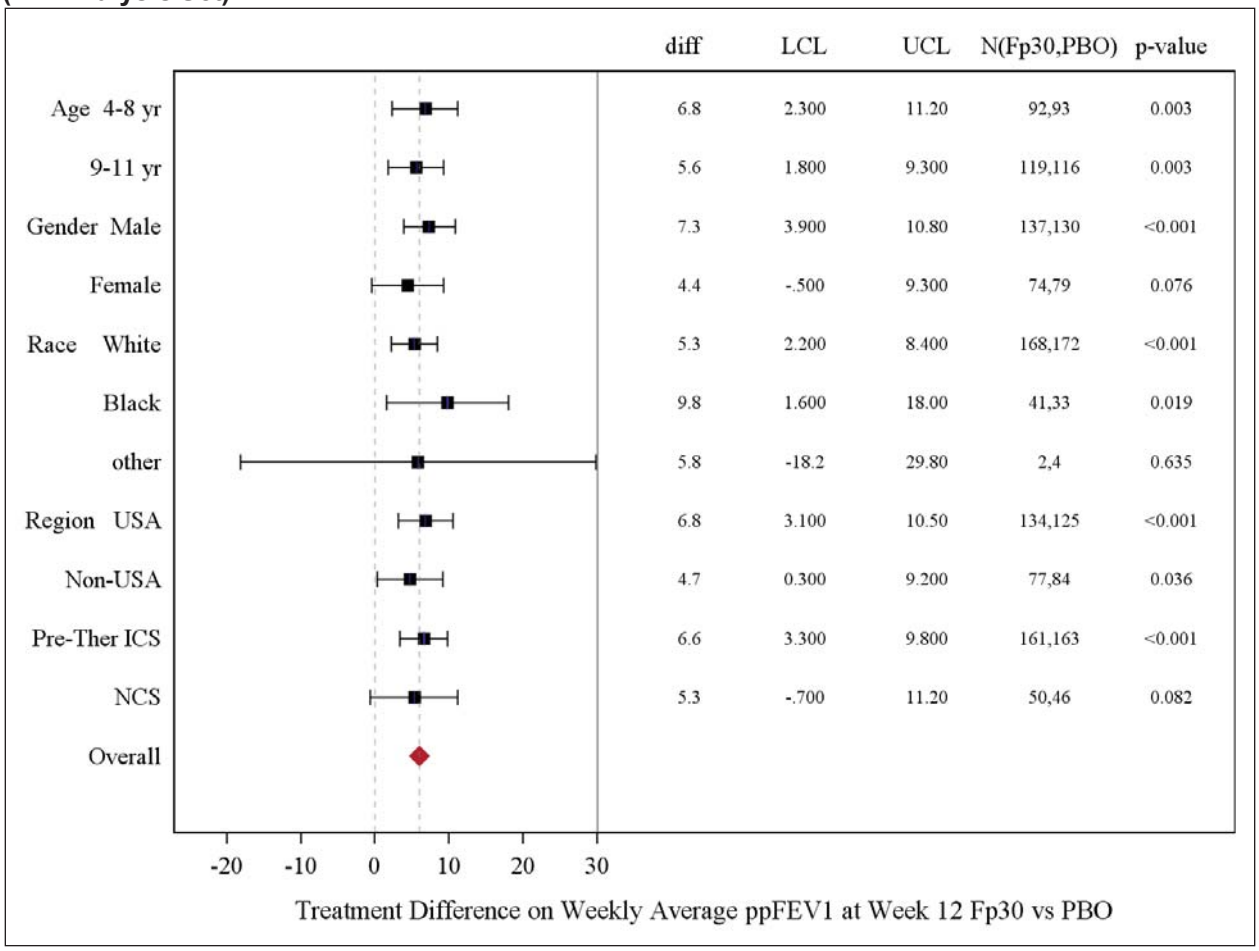
Figure 7. Forest Plot of Subgroup Analysis of Co-Primary Endpoint of Change From Baseline in Weekly Average of Percent Predicted Morning Trough FEV1 at Week 12 Fp 55 mcg Versus Placebo (ITT Analysis Set)



Source: Statistical Reviewer

Abbreviations: diff, difference; FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; ICS, inhaled corticosteroid; ITT, intent-to-treat; LCL, lower control limit; N, number; NCS, no corticosteroid; PBO, placebo; ppFEV1, percent predicted forced expiratory volume in 1 second; Ther, therapy; UCL, upper control limit; USA, United States of America; yr; year

Figure 8. Forest Plot of Subgroup Analysis of Co-Primary Endpoint of Change From Baseline in Weekly Average of Percent Predicted Morning Trough FEV1 at Week 12 Fp 30 mcg Versus Placebo (ITT Analysis Set)



Source: Statistical Reviewer
Abbreviations: diff, difference; FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; ICS, inhaled corticosteroid; ITT, intent-to-treat; LCL, lower control limit; N, number; NCS, no corticosteroid; PBO, placebo; ppFEV1, percent predicted forced expiratory volume in 1 second; Ther, therapy; UCL, upper control limit; USA, United States of America; yr; year

Integrated Review of Effectiveness

8.1.3. Integrated Assessment of Effectiveness

In this supplemental NDA, the Applicant has submitted results from Trial 30003, a 12-week randomized, double-blind, placebo-controlled, parallel group trial in 841 patients aged 4 to 11 years old with persistent asthma. For the first co-primary endpoint of change from baseline in 1-hour post-dose FEV1 at 12-weeks for FS 55/14 mcg versus Fp 55 mcg comparison, to demonstrate the contribution of the salmeterol monocomponent to the combination, results were not statistically significant (Table 16). Results across all secondary endpoints for the FS 55/14 mcg to Fp 55 mcg comparison are consistent with the first co-primary endpoint (Table 19). These data suggest that the salmeterol monocomponent does not contribute to the effect of FS 55/14 mcg in terms of efficacy. As this contribution must be demonstrated to support efficacy, data from trial 30003 are insufficient to support the efficacy of FS 55/14 mcg.

With regard to the second co-primary endpoint of change from baseline in the weekly average of tFEV1 of Fp 55 mcg compared to placebo, results demonstrated that treatment with Fp 55 mcg demonstrated improvements compared to placebo. While the 95% CI excluded null and the nominal p-value was <0.05, this results cannot be considered statistically significant (Table 16) due to failure earlier in the analysis hierarchy. Secondary endpoint results for Fp 55 mcg were consistent with the second co-primary endpoint with the majority demonstrating that Fp 55 mcg treatment resulted in numerically greater improvements versus placebo with 95% CIs excluding null. Results for the Fp 30 mcg versus placebo comparison mirrored the Fp 55 mcg results (Table 20). While results for the Fp doses cannot be considered statistically significant, they are strongly suggestive of efficacy. As such, data from this trial, taken together with the clear efficacy previously demonstrated for Fp in the adolescent/adult program, is sufficient to support the efficacy of Fp 30 mcg and 55 mcg in the 4 to 11-year-old population.

8.2. Review of Safety

8.2.1. Safety Review Approach

Trial 30003 was the sole trial used in the evaluation of safety in patients aged 4 to 11 years old. Applicant data was verified, and independent safety analyses were conducted by this reviewer using Analysis Studio software, version 1.4.2 and JMP 15. Safety analysis was conducted on the safety analysis set unless specified otherwise in the table heading.

8.2.2. Review of the Safety Database

Overall Exposure

In Trial 30003, a total of 839 patients were included in the safety analysis set, which was comprised of all patients who received at least one dose of study drug. The safety analysis set differs from the ITT population, as two patients who were randomized to Fp 55mcg did not receive drug. Of the 839 patients in the safety analysis set, 630 were exposed to Fp 30mcg (n=211), Fp 55mcg (n=208), or FS 55/14 mcg (n=211). Exposures were comparable across treatment groups. The mean duration of exposure overall was 81.7 days, with a median exposure of 85 days. Compliance was also generally similar between treatment arms. These data are summarized in Table 21.

Table 21. Study Drug Exposure

		Fp MDPI		FS MDPI
Variable	Placebo (N=209)	30 mcg BID (N=211)	55 mcg BID (N=208)	55/14 mcg BID (N=211)
Time treated, n (%)				
≤2 weeks	6 (3)	7 (3)	4 (2)	1 (<1)
>2 to ≤4 weeks	5 (2)	0	3 (1)	3 (1)
>4 to ≤8 weeks	9 (4)	5 (2)	4 (2)	6 (3)
>8 to ≤12 weeks	185 (89)	192 (91)	192 (92)	192 (91)
>12 weeks	4 (2)	7 (3)	5 (2)	9 (4)

Variable	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)
Duration of treatment (days)				
n	209	211	208	211
Mean	79.7	81.9	82.0	83.2
SD	17.07	14.63	14.38	10.88
Median	85.0	85.0	85.0	85.0
Minimum, maximum	1, 97	1, 104	2, 104	5, 98

Source: Trial 3003 Clinical Study Report, table 14; page 104-105.
Abbreviations: BID, twice daily; Fp, fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with specified treatment time; SD, standard deviation.

Adequacy of the safety database:

Overall, the safety database is of sufficient size and duration for 4-to-11-year-olds with persistent asthma, given the experience with fluticasone propionate and salmeterol specifically, and inhaled corticosteroids and long-acting beta agonists in general, in a similar population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues with data integrity and submission quality identified in the review of this supplemental NDA. There were no site inspections due to the low safety concern and the ongoing coronavirus pandemic. See Section 4.1.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocol. AEs were defined as per regulatory requirements. Adverse events were captured after the signing of informed consent through the end of the follow-up period, defined as approximately 7 days after the last dose of study drug. Treatment emergent adverse events (TEAEs) were any adverse events that increased in severity or that were newly developed at or after the first dose of study drug through the end of the follow-up period. AEs and TEAEs were key safety assessments and were summarized by treatment, MedDRA System Organ Class (SOC) and Preferred Term (PT). Patients were counted only once in each PT and SOC category. AEs were coded using the MedDRA dictionary version 21.0. Grading of AE severity was mild/moderate/severe with appropriate definitions of each category for the patient population. The Applicant's coding of preferred terms (PTs) was appropriate. The Applicant collected data on asthma exacerbations and oropharyngeal examinations as safety outcomes of interest, in addition to vital signs and physical examinations.

Routine Clinical Tests

Clinical laboratory parameters other than pregnancy tests were not routinely assessed in Trial 30003. Human chorionic gonadotropin tests in urine were performed for all female patients who reached puberty and achieved menarche at screening and, if clinically indicated,

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 208798-S08 Fluticasone proprionate (ArmonAir) and NDA 208799-(b) (4) S21 Fluticasone propionate/salmeterol (AirDuo)}

thereafter.

8.2.4. Safety Results

Deaths

There were no deaths during Trial 30003.

Serious Adverse Events

Serious adverse events (SAE) were not common. A total of eight patients experienced nine treatment emergent SAEs during Trial 30003. These events were isolated and occurred in single patients, except for asthma. The pattern of SAEs did not reveal any new safety concerns. Serious adverse events are displayed in Table 22.

Table 22. Serious Adverse Events

		Fp MDPI		FS MDPI
System Organ Class/Preferred Term, n (%)	Placebo (N=209)	30 mcg BID (N=211)	55 mcg BID (N=208)	55/14 mcg BID (N=211)
Patients with at least 1 SAE	1 (<1)	2 (<1)	1 (<1)	4 (1.9)
Blood and lymphatic system disorders	0	0	0	1
Lymphadenitis	0	0	0	1
General disorders and administration site conditions	0	0	0	1
Pyrexia	0	0	0	1
Infections and infestations	1 (<1)	1 (<1)	0	0
Pneumonia mycoplasmal	0	1	0	0
Respiratory tract infection viral	1	0	0	0
Nervous system disorders	0	0	0	2 (<1)
Headache	0	0	0	1 (<1)
Partial seizures	0	0	0	1 (<1)
Psychiatric disorders	0	0	1 (<1)	0
Disruptive mood dysregulation disorder	0	0	1 (<1)	0
Respiratory, thoracic, and mediastinal disorders	1 <1)	1 (<1)	0	0
Asthma	1 <1	1 (<1)	0	0

Source: Applicant Clinical trial Report, table 15.3.2.5, page 422
Abbreviations: BID, twice daily; Fp, Fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with specified SAE; SAE, serious adverse event

Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations of treatment due to adverse events were not common (Table 23). A total of 8 patients discontinued study treatment due to an AE. AEs leading to discontinuation were most common in the placebo arm (6%), and least common in the Fp 55 mcg arm (n=3%). Aside from asthma, only one AE leading to discontinuation occurred in >1 patient (upper respiratory infection). These results do not raise new safety concerns.

Table 23. Adverse Events Leading to Treatment Discontinuation

System Organ Class/ Preferred Term, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)
Patients with at least 1 AE causing discontinuation	13 (6)	8 (4)	6 (3)	6 (3)
Infections and infestations	0	2 (<1)	1 (<1)	0
Upper respiratory tract infection	0	2 (<1)	1 (<1)	0
Nervous system disorders	0	0	0	2 (<1)
Aphonia	0	0	0	1 (<1)
Headache	0	0	0	1 (<1)
Psychiatric disorders	0	0	1 (<1)	0
Disruptive mood dysregulation disorder	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	13 (6)	6 (3)	4(2)	4 (2)
Asthma	13 (6)	6 (3)	4 (2)	4 (2)
Epistaxis	0	1 (<1)	0	0

Source: Response to information request dated 5/17/2021; table 1

Abbreviations: AE, adverse event; BID, twice daily; Fp, Fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with specified AE

Significant Adverse Events

In Trial 30003, the majority of TEAEs were mild or moderate. Severe AEs were not common with a total of 4 severe AEs reported in 4 patients. The severe AEs were as follows:

- Patient (b) (6) (FP MDPI 55 mcg): Bronchitis occurred on study day 4 and resolved on study day 16.
- Patient (b) (6) (FS MDPI 55/14 mcg): Pyrexia occurred on study day 103 and resolved on study day 119.
- Patient (b) (6) (FS MDPI 55/14 mcg): Partial seizures occurred on study day 49. The event duration was reported as 5 minutes, and the event resolved.
- Patient (b) (6) (FS MDPI 55/14 mcg): Headache occurred on study day 50.

More patients in the FS 55/14 mcg group experienced a severe AE compared to other treatment groups. However, given the small number of events, definitive conclusions cannot be made.

Safety analyses were also performed for moderate and severe adverse events. Moderate to severe AEs were reported in 16-22% of patients across all treatment groups. In general, events were numerically balanced between arms and occurred in <1% of patients. The most common moderate to severe AE occurred in the infections and infestations SOC, with the most common preferred term of respiratory tract infection. This is not unexpected given the studied age group. Analyses of these events did not reveal new safety concerns. Data for moderate to severe AEs are summarize in Table 24.

Table 24. Moderate and Severe Adverse Events

System Organ Class/ Preferred Term, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)
Patients with at least 1 moderate or severe AE	47 (22)	35 (17)	29 (14)	33 (16)
Blood and lymphatic system disorders	1 (<1)	0	0	0
Lymphadenitis	1 (<1)	0	0	0
Gastrointestinal disorders	2 (<1)	2 (<1)	3 (1)	1 (<1)
Diarrhea	1 (<1)	1 (<1)	0	1 (<1)
Vomiting	1 (<1)	0	2 (<1)	0
Nausea	0	0	2 (<1)	0
Abdominal pain upper	0	0	1 (<1)	0
Fecaloma	0	0	1 (<1)	0
Toothache	0	1 (<1)	0	0
General disorders and administration site conditions	1 (<1)	2 (<1)	0	1 (<1)
Pyrexia	0	2 (<1)	0	1 (<1)
Malaise	1 (<1)	0	0	
Immune system disorders	1 (<1)	1 (<1)	1 (<1)	0
Dust allergy	0	1 (<1)	0	0
Food allergy	1 (<1)	0	0	0
Seasonal allergy	0	0	1 (<1)	0
Infections and infestations	28 (13)	19 (9)	21 (10)	24 (11)
Respiratory tract infection viral	4 (2)	4 (2)	6 (3)	6 (3)
Upper respiratory tract infection	4 (2)	1 (<1)	2 (<1)	6 (3)
Nasopharyngitis	4 (2)	2 (<1)	2 (<1)	2 (<1)
Pharyngitis streptococcal	4 (2)	2 (<1)	2 (<1)	1 (<1)
Influenza	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Pharyngitis	0	1 (<1)	2 (<1)	2 (<1)
Bronchitis	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Otitis media	0	1 (<1)	2 (<1)	1 (<1)
Respiratory tract infection	2 (<1)	0	1 (<1)	1 (<1)
Tonsillitis	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Ear infection	1 (<1)	0	1 (<1)	1 (<1)
Pneumonia	1 (<1)	0	0	2 (<1)
Sinusitis	2 (<1)	0	0	1 (<1)
Viral upper respiratory tract infection	1 (<1)	0	1 (<1)	1 (<1)
Tracheitis	0	2 (<1)	0	0
Acute sinusitis	1 (<1)	0	0	0
Conjunctivitis	0	0	1 (<1)	0
Croup infectious	1 (<1)	0	0	0
Gastroenteritis	1 (<1)	0	0	0
Laryngitis viral	1 (<1)	0	0	0
Otitis externa	1 (<1)	0	0	0
Otitis media acute	0	1 (<1)	0	0
Peritonsillar abscess	0	1 (<1)	0	0
Pneumonia mycoplasmal	0	1 (<1)	0	0
Rhinitis	0	1 (<1)	0	0
Sinusitis bacterial	1 (<1)	0	0	0
Tracheobronchitis	0	0	1 (<1)	0
Varicella	1 (<1)	0	0	0
Viral tracheitis	1 (<1)	0	0	0

System Organ Class/ Preferred Term, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)
Injury, poisoning and procedural complications	2 (<1)	3 (1)	0	0
Clavicle fracture	1 (<1)	0	0	0
Concussion	1 (<1)	0	0	0
Humerus fracture	0	1 (<1)	0	0
Laceration	0	1 (<1)	0	0
Limb injury	0	1 (<1)	0	0
Nervous system disorders	1 (<1)	1 (<1)	1 (<1)	3 (1)
Headache	0	1 (<1)	1 (<1)	2 (<1)
Partial seizures	0	0	0	1 (<1)
Psychiatric Disorders	0	0	1 (<1)	0
Disruptive mood dysregulation disorder	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	21 (10)	(5)	6 (3)	4 (2)
Asthma	16 (8)	6 (3)	4 (2)	4 (2)
Cough	2 (<1)	3 (1)	0	0
Epistaxis	0	1 (<1)	1 (<1)	0
Rhinitis allergic	2 (<1)	0	0	0
Nasal congestion	0	1 (<1)	0	0
Oropharyngeal pain	0	1 (<1)	0	0
Oropharyngeal spasm	0	0	1 (<1)	0
Pneumonitis	1 (<1)	0	0	0
Skin and subcutaneous disorders	1 (<1)	2 (<1)	0	1 (<1)
Urticaria	1 (<1)	1 (<1)	0	0
Dermatitis atopic	0	1 (<1)	0	0
Eczema	0	0	0	1 (<1)

Source: Response to information request dated 5/17/2021; table 3
Abbreviations: BID, twice daily; AE, adverse event; Fp, Fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with specified AE

Treatment Emergent Adverse Events and Adverse Reactions

Approximately 41% of patients experienced a TEAE. Across treatment groups incidence ranged from 37-45% with the most events occurring the Fp 30mcg and 55mcg groups. The most commonly reported TEAE occurred in the infections and infestations SOC, with the most common PTs being nasopharyngitis, upper respiratory tract infection, and respiratory tract infection. TEAEs in the infection and infestation SOC occurred most commonly in the Fp 55 mcg group and was driven by events such as respiratory tract infection and respiratory tract infection viral. However, otherwise TEAEs were fairly balance across treatment arms. These data are summarized in Table 25.

Table 25. Treatment-Emergent Adverse Events That Occurred in ≥2% of Patients in Any Treatment Group

System Organ Class/ Preferred Term, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)	Total (N=839)
Patients with at least 1 TEAE	92 (44)	99 (47)	95 (46)	82 (39)	368 (44)
Gastrointestinal disorders	6 (3)	12 (6)	9 (4)	9 (4)	36 (4)
Nausea	0	1 (<1)	4 (2)	0	5 (<1)

System Organ Class/ Preferred Term, n (%)	Placebo (N=209)	Fp MDPI 30 mcg BID (N=211)	Fp MDPI 55 mcg BID (N=208)	FS MDPI 55/14 mcg BID (N=211)	Total (N=839)
General disorders and administration site conditions	3 (1)	6 (3)	4 (2)	1 (<1)	14 (2)
Pyrexia	0	5 (2)	3 (1)	1 (<1)	9 (1)
Infections and infestations	61 (29)	60 (28)	73 (35)	57 (27)	251 (30)
Nasopharyngitis	11 (5)	8 (4)	11 (5)	9 (4)	39 (5)
Upper respiratory tract infection	9 (4)	10 (5)	8 (4)	10 (5)	37 (4)
Respiratory tract infection	7 (3)	3 (1)	10 (5)	5 (2)	25 (3)
Respiratory tract infection viral	7 (3)	7 (3)	10 (5)	8 (4)	32 (4)
Bronchitis	5 (2)	(2 <1)	4 (2)	2 (<1)	13 (2)
Pharyngitis streptococcal	4 (2)	3 (1)	5 (2)	1 (<1)	13 (2)
Pharyngitis	3 (1)	10 (5)	8 (4)	9 (4)	30 (4)
Viral infection	2 (<1)	0	0	4 (2)	6 (<1)
Viral upper respiratory tract infection	2 (<1)	1 (<1)	5 (2)	3 (1)	11 (1)
Influenza	1 (<1)	5 (2)	2 (<1)	4 (2)	12 (1)
Otitis media	0	1 (<1)	4 (2)	2 (<1)	7 (<1)
Nervous system disorders	3 (1)	4 (2)	4 (2)	5 (2)	16 (2)
Headache	2 (<1)	4 (2)	4 (2)	3 (1)	13 (2)
Respiratory, thoracic and mediastinal disorders	29 (14)	30 (14)	12 (6)	19 (9)	90 (11)
Asthma	21 (10)	11 (5)	6 (3)	8 (4)	46 (5)
Cough	5 (2)	10 (5)	0	1 (<1)	16 (2)
Rhinitis allergic	4 (2)	5 (2)	3 (1)	2 (<1)	14 (2)
Epistaxis	0	1 (<1)	2 (<1)	4 (2)	7 (<1)

Source: Response to information request dated 5/17/2021; table 4

Abbreviations: BID, twice daily; TEAE, treatment emergent adverse event; Fp, Fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of patients in study arm; n, number of patients with specified AE

Laboratory Findings

Clinical laboratory parameters other than pregnancy tests were not routinely assessed in Trial 30003. No patient had a positive pregnancy test during Trial 30003.

Vital Signs

Vital signs (pulse, systolic blood pressure and diastolic blood pressure) were assessed at baseline and each visit. There were no clinically meaningful trends in mean changes from baseline for any of these variables. There were no serious adverse events reported related to vital signs variables. One patient (ID number (b) (6)) in the Fp 30 mcg group experienced an adverse event of mild hypertension on study day 57 that resolved on study day 86.

Physical examination

Physical examination findings were assessed at baseline and at week 12. Shifts from normal to abnormal were seen in each treatment group for chest and lungs, HEENT, and skin. These shifts to abnormal from baseline occurred for a similar number of patients in each treatment group.

The greatest number of shifts to abnormal from baseline was reported for chest and lungs, followed by HEENT, and then skin. The greatest number of shifts to abnormal from baseline for chest and lungs occurred in the placebo group (23 patients), for HEENT in the Fp 30 mcg group (18 patients), and for skin in the placebo group (7 patients). These shifts are unexpected for the patient population and do not raise a safety concern.

Electrocardiograms (ECGs)

Electrocardiography was not collected for this study.

QT

The arythmogenic potential was assessed in the initial NDA review cycle. The approved labels for Fp (ArmonAir) and fluticasone propionate/salmeterol (FS, AirDuo) include discussion of effects of the drugs on QT interval. Further exploration of QT was not conducted in Trial 30003.

8.2.5. Analysis of Submission-Specific Safety Issues

Given the known safety concerns with this product and the patient population, specific safety analyses were performed for asthma exacerbations, local effects (i.e., oral candidiasis), paradoxical bronchospasm, and systemic glucocorticoid effects.

8.2.5.1. Asthma exacerbations

Asthma exacerbations were more commonly reported in the placebo group compared active treatment groups overall, based on exacerbation severity, and exacerbations resulting in treatment discontinuation or hospitalization. These data are summarized in Table 26. These data do not raise safety concerns.

Table 26. Asthma Exacerbations by Severity and Treatment Group

		Fp MDPI		FS MDPI
Category, n (%)	Placebo (N=209)	30 mcg BID (N=211)	55 mcg BID (N=208)	55/14 mcg BID (N=211)
Patients with at least 1 asthma exacerbation				
All	22 (11)	12 (5.6)	6 (2.9)	8 (3.8)
Mild	5 (2.3)	5 (2.3)	2 (1)	4 (1.9)
Moderate	17 (8.1)	6 (2.8)	3 (1.4)	4 (1.9)
Severe	0	1 (0.5)	1 (0.5)	0
Patients with at least 1 asthma exacerbation resulting in discontinuation of treatment				
All	13 (6.2)	5 (2.4)	4 (1.9)	4 (1.9)
Mild	3 (1.4)	2 (0.9)	1 (0.5)	1 (0.5)
Moderate	10 (4.8)	2 (0.9)	2 (1)	3 (1.4)
Severe	0	1 (0.5)	1 (0.5)	0

		Fp MDPI		FS MDPI
Category, n (%)	Placebo (N=209)	30 mcg BID (N=211)	55 mcg BID (N=208)	55/14 mcg BID (N=211)
Patients with at least 1 asthma exacerbation resulting in hospitalization				
All	1 (0.5)	2 (0.9)	0	0
Mild	1 (0.5)	1 (0.5)	0	0
Moderate	0	0	0	0
Severe	0	1 (0.5)	0	0
Proportion of patients discontinuing study drug for asthma exacerbations, n/M (%)	13/208 (6)	5/210 (2)	3/208 (1)	4/211 (2)

Source: Applicant Clinical Trial Report, Table 25, page 121 and Table 41, pages 156-157. Reviewer verified.
If a patient reports more than 1 asthma exacerbation, the reatest severity is presented.
Abbreviations: BID, twice daily; Fp, Fluticasone propionate; FS, fluticasone propionate/salmeterol; MDPI, multidose dry powder inhaler; N, number of subjects in study arm; n, number of subjects with specified condition

8.2.5.2. Local Effects and Paradoxical Bronchospasm

To assess for local effects of corticosteroids, oropharyngeal examinations were performed at baseline and at each visit. Positive swab test results for Candida culture were reported for 6 patients overall, 2 each in the placebo group, Fp 30 mcg group and Fp 55 mcg group. This finding is expected, given the known and labeled safety profile for ICS and patient population. This does not raise a new safety concern.

As this is an inhaled product, paradoxical bronchospasm with administration is a known concern. However, there were no adverse events of bronchospasm or laryngeal spasm reported to suggest the occurrence of paradoxical bronchospasm. This does not raise a new safety concern.

8.2.5.3. Systemic Glucocorticoid Effects

As this product is a glucocorticoid (GC), there is the theoretical risk of systemic GC effects. However, as the systemic exposure to fluticasone propionate following inhalation is similar to the approved Advair product (see section 6), any systemic effects would be likely be consistent with the approved product. As such this product does not raise new safety concerns regarding systemic GC effects.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Two clinical outcome assessment tools were collected in trial 30003, the Childhood Asthma Control Test (C-ACT) and asthma symptom scores. The C-ACT is a caregiver and patient completed clinical outcome assessment tool that was assessed as a secondary efficacy endpoint in Trial 30003. Asthma symptom scores were recorded by patients and caregivers in the electronic diary portion of the handheld spirometer device. The change from baseline in the C-

ACT score and the change from baseline in the weekly average total daily (daytime and nighttime) asthma symptom score was a secondary efficacy endpoint in Trial 30003 and is discussed in Section 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were conducted for sex, race, and age group (4-to-8-year-olds and 9-to-11-year-olds). Generally, these analyses were reflective of the adverse events in the general population of Trial 30003. These analyses did not reveal new safety concerns.

8.2.8. Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

The Applicant did not include bone mineral density measurements, formal hypothalamic–pituitary–adrenal (HPA) axis and growth studies in the adult or pediatric clinical development program for Fp and FS as the systemic exposure for these proposed products are lower or similar to the marketed products (see section 6). Also refer to the primary clinical review for NDA 208798 and 208799 dated October 26, 2016.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The study drugs did not have abuse and addiction potential.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Fluticasone propionate as Teva's ArmonAir Respiclick and fluticasone propionate/salmeterol as Teva's AirDuo RespiClick and Digihalers were initially approved on January 27, 2017 for the maintenance treatment of asthma in patients 12 years and older. Since that time until the date of this review no new issues have been identified that would alter the risk-benefit profile in the approved indication. Additionally, the safety profile for inhaled fluticasone propionate and salmeterol in this patient population is well-known, as the same active moieties delivered via the inhaled route have been marketed for over 2 decades (e.g., Flovent, Advair).

Expectations on Safety in the Postmarket Setting

Fp and FS are subject to standard post-marketing safety reporting prior to the submission of this supplemental NDA. The Applicant has been providing adequate reporting including annual safety reports. No new safety signals have been identified as of the most recent annual report reviewed, dated March 26, 2021. The patient population in Trial 30003 is generally similar to the target population. Given this fact and the postmarketing experience, no substantial differences are anticipated.

8.2.10. Integrated Assessment of Safety

The safety data submitted with this supplemental NDA was sufficient to assess the safety of Fp and FS in the proposed patient population. The safety information for Fp and FS in 4 to 11-year-old patients is based on Trial 30003. No deaths occurred. Eight patients had nine serious adverse events during Trial 30003. The serious treatment emergent adverse events are typical of the patient population. There were a total of 8 treatment discontinuations due to adverse events in Trial 30003, that did not raise a safety concern. The SAE and AE profiles are typical for the population studied and consistent with the known safety profile of Fp and FS. Overall, no new safety signals were identified for Fp and FS. The safety profile of Fp 30 mcg, Fp 55 mcg and FS 55/14 mcg in the 4 to 11-year-old age group with persistent asthma is favorable.

8.3. Statistical Issues

Substantial evidence of effectiveness

For the first co-primary endpoint, change from baseline in 1-hour post-dose morning ppFEV1 at week 12, FS 55/14 mcg did not demonstrate statistically significant difference from Fp 55 mcg.

Across all secondary efficacy endpoints, for the comparison of FS 55/14 mcg versus Fp 55 mcg, the 95% CIs included null. These results are consistent with the first co-primary endpoint. The contribution of the salmeterol component to FS 55/14 mcg has not been demonstrated. Therefore, these data do not provide support for the efficacy of FS 55/14 mcg. We conclude that substantial evidence of effectiveness of FS 55/14 mcg versus Fp 55 mcg was not demonstrated in this study.

For the second co-primary endpoint, the change from baseline in weekly average of the trough morning ppFEV1 at week 12, both Fp 55 mcg and Fp 30 mcg results showed numerical improvements compared to placebo with 95% CIs excluding null. While these results cannot be considered statistically significant due to failure at the first co-primary endpoint, these Fp data provide some support for the efficacy of Fp at both doses.

With regard to secondary endpoints results for Fp to placebo comparisons, results were generally consistent with the second co-primary endpoint. For the majority, results for both Fp doses demonstrated differences from placebo. Specifically, the following endpoints were supportive of an Fp versus placebo effect for both Fp 30 mcg and Fp 55 mcg doses: change from baseline in weekly average of daily trough morning PEF over 12 weeks, change from baseline in weekly average of total daily use of albuterol/salbutamol over weeks 1 through 12, change from baseline in weekly average of total daily asthma symptom score over weeks 1 through 12. The secondary endpoint of change from baseline in asthma control (measured by C-ACT) over the 12-week treatment period was supportive for the Fp 30 mcg dose but not for the Fp 55 mcg dose. The following endpoints were not supportive of either dose: time to onset of effect in daily rescue medication use, and proportion of patients who discontinued from study drug for asthma exacerbation during the 12-week treatment period.

In summary, the effectiveness of both doses Fp versus placebo was demonstrated for the second co-primary endpoint and supported by most of the secondary endpoints examined. We conclude that substantial evidence of effectiveness of Fp 55 mcg versus placebo and Fp 30 mcg versus placebo were reasonably demonstrated in this study.

Treatment policy estimand versus on treatment estimand

In this study all the primary analyses targeted on-treatment estimand. The applicant used data collected while patients on-treatment in the analyses. This is not a desirable approach from a regulatory perspective. The regulatory recommended estimand is treatment-policy estimand. Under this estimand, the analyses use all data collected regardless any intercurrent events.

For patients who discontinue study treatment, the applicant stated that they will encourage the patient to continue in the study and return for planned visits until the study completion in order to collect data after study treatment discontinuation. However, these collected data was not included in the primary efficacy analyses.

This reviewer examined robustness of the efficacy results under treatment-policy estimand. For the recommendation to approve Fp 30 mcg and Fp 55 mcg, we have compared efficacy results on the second co-primary endpoint under both on-treatment estimand and treatment policy-estimand. Results are presented in Table 27. From Table 27, we conclude that results under on-treatment estimand and treatment-policy estimand are qualitatively the same. Thus, this reviewer concludes that efficacy of Fp 55 mcg versus placebo and Fp 30 mcg versus placebo are robust regardless of on-treatment estimand or treatment-policy estimand.

Table 27. Comparison of Treatment Effect Under On-Treatment Estimand and Treatment Policy Estimand on Endpoint of Change From Baseline in Weekly Average of Percent Predicted Morning Trough FEV1 at Week 12 (ITT Analysis Set)

	Fp MDPI LSM (95% CI) p-value	
Endpoint	**On-Treatment Estimand**	**Treatment Policy Estimand**
CFB in weekly average of the trough morning ppFEV1 at Week 12 Fp 55 mcg vs placebo: %	7.0 (4.1, 9.8) <0.001	6.2 (3.4, 9.1) <0.001
CFB in weekly average of the trough morning ppFEV1 at Week 12 Fp 30 mcg vs placebo: %	6.0 (3.2, 8.8) <0.001	5.4 (2.5, 8.2) <0.001

Source: Statistical Reviewer
Abbreviations: CFB, change from baseline; CI, confidence interval; FEV1, forced expiratory volume in 1 second; Fp, fluticasone propionate; ITT, intent-to-treat; LSM, least squares mean; MDPI, multidose dry powder inhaler; ppFEV1, percent predicted forced expiratory volume in 1 second

Multiplicity control

The multiplicity was not strongly controlled among all the secondary endpoints. However, for most of the secondary endpoints examined, the hypothesis testing p-value for comparison

between Fp doses versus placebo is less than 0.001. The Applicant didn't make any label claim on any secondary endpoints. This reviewer concludes that multiplicity control was reasonable.

8.4. Conclusions and Recommendations

(b) (4)

The regulatory action to be taken for FS 55/14 mcg NDA 208799-S21 is Approval.

The regulatory action to be taken is Approval for Fp for the treatment of asthma in 4 to 11-year olds at the doses of Fp 30 mcg orally inhaled BID and Fp 55 mcg orally inhaled BID (NDA 208798-S08).

In these supplemental NDAs, the Applicant has submitted an analysis of Trial 30003, a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of fluticasone propionate (Fp) Multidose Dry Powder Inhaler (MDPI) 30 mcg and 55 mcg administered twice daily and fluticasone propionate/salmeterol (FS) Multidose Dry Powder Inhaler (MDPI) 55/14 mcg administered twice daily in patients aged 4 through 11 years old with persistent asthma. For the first co-primary endpoint of change from baseline in 1-hour post-dose FEV1 at 12-weeks for FS 55/14 mcg versus Fp 55 mcg comparison, to demonstrate the contribution of the salmeterol monocomponent to the combination, results were not statistically significant (Table 16). Results across all secondary endpoints for the FS 55/14 mcg to Fp 55 mcg comparison are consistent with the first co-primary endpoint (Table 19). These data suggest that the salmeterol monocomponent does not contribute to the effect of FS 55/14 mcg in terms of efficacy. As this contribution must be demonstrated to support efficacy, data from trial 30003 are insufficient to support the efficacy of FS 55/14 mcg.

With regard to the second co-primary endpoint of change from baseline in the weekly average of tFEV1 of Fp 55 mcg compared to placebo, results demonstrated that treatment with Fp 55 mcg demonstrated improvements compared to placebo. While the 95% CI excluded null and the nominal p-value was <0.05, this result cannot be considered statistically significant (Table 16) due to failure earlier in the analysis hierarchy. Secondary endpoint results for Fp 55 mcg were consistent with the second co-primary endpoint with the majority demonstrating that Fp 55 mcg treatment resulted in numerically greater improvements versus placebo with 95% CIs excluding null. Results for the Fp 30 mcg versus placebo comparison mirrored the Fp 55 mcg results (Table 20). While results for the Fp doses cannot be considered statistically significant, they are strongly suggestive of efficacy. As such, data from this trial, taken together with the clear efficacy previously demonstrated for Fp in the adolescent/adult program, is sufficient to support the efficacy of Fp 30 mcg and 55 mcg in the 4 to 11-year-old population.

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 208798-S08 Fluticasone proprionate (ArmonAir) and NDA 208799-(b) (4)S21 Fluticasone propionate/salmeterol (AirDuo)}

Data from Trial 30003 did not reveal any new safety signals. Additionally, results from PK trial 10007 demonstrated that exposure to fluticasone propionate and salmeterol were comparable or lower in patients administered Fp 55 mcg and FS 55/14 mcg compared to Advair.

The overall risk-benefit assessment supports approval of Fp 30 mcg and Fp 55 mcg in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. The regulatory action to be taken for the Fp 30 mcg and Fp 55 mcg sNDA is Approval.

The overall risk-benefit assessment of FS 55/14 mcg does not support the use of FS 55/14 mcg in 4 to 11-year olds with persistent asthma as the contribution of the salmeterol component was not demonstrated. (b) (4)

While trial results did not provide substantial evidence of efficacy for FS 55/14mcg in patients 4 to 11 years of age, Trial 30003 was a PREA PMR trial and conducted under a Written Request. Therefore, section 8.4 of the FS label will be amended to state that the safety and efficacy of FS 55/14 mcg has not been demonstrated in the 4 to 11 year old population. (b) (4) the addition of pediatric data to section 8.4 will be taken under sNDA 208799-S21, as a labeling supplement with clinical data.

The overall risk-benefit assessment supports approval of Fp 30 mcg and Fp 55 mcg in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. The regulatory action to be taken for the Fp 30 mcg and Fp 55 mcg sNDA 208798-S08 is Approval.

Trials 30003 and 10007 also satisfied the PREA PMR trials 3154-2/3155-2 and 3154-1/3155-1, respectively.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not necessary for this supplemental NDA.

10 Pediatrics

Trials 30003 and 10007 were conducted entirely in pediatric patients.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Results from Trial 30003 did not provide substantial evidence of efficacy for FS 55/14mcg in patients 4 to 11 years of age (b) (4) However, as Trial 30003 was a PREA PMR trial, verbiage was included in section 8.4 stating that the safety and efficacy of FS 55/14 mcg had not been demonstrated in the 4 to 11 year old population. (b) (4) and the section 8.4 changes were made under sNDA 208799-S21.

Based on results from Trials 30003 and 10007, the Applicant proposed to amend the Fp label to expand the indicated population to include 4 to 11 years olds at a dose of 30mcg or 55mcg twice daily (sNDA 208798-S08). This was acceptable. The sponsor also proposed to amend the label include results from these trials in sections 6, 8, 12, and 14. The proposed changes to these sections were edited by the Division for brevity, clarity, and consistency with current labeling practice. The Applicant's initial proposed edits to section 14 were expansive (b) (4) the Division edited down the proposed content significantly, including only the secondary co-primary endpoint results which compared Fp 30 and 55mcg to placebo.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not needed for this supplemental NDA.

13 Postmarketing Requirements and Commitment

None are required for this supplemental NDA.

14 Deputy Division Director (Clinical, designated signatory authority) Comments

In these supplemental NDAs (sNDA), the Applicant sought the extension of the asthma indication to the 4-11 year old age group. A single trial (Trial 30003) included both fluticasone/salmeterol and two doses of fluticasone propionate, with co-primary endpoints to determine the efficacy of each product. Trial 30003 was the conducted fulfill PREA post-marketing requirements (PMRs) for both products, and was also the subject of Written Request (WR). The PREA PMRs and WR have been fulfilled.

With regard to FS, the Applicant has not demonstrated the contribution of salmeterol to the fluticasone/salmeterol component, as evidenced by failure at the first co-primary endpoint. Therefore, efficacy of FS has not been demonstrated in children 4-11 years of age (b) (4) the required update to labeling to reflect that efficacy was not demonstrated for FS in pediatric patients, respectively. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments (b) (4). However as Trial 30003 was conducted to fulfill a PREA PMR and was the subject of a Written Request, section 8.4 of the package insert has been amended to include information relaying that efficacy of this product was not demonstrated in patients 4-11 years of age. With regard to section 8.4 labeling changes, (b) (4) labeling changes will be made under sNDA 209799-S21. (b) (4) The action for sNDA 208799-S21 will be ***Approval.***

With regard to Fp, despite issues with the statistical hierarchy, Trial 30003 demonstrated the efficacy fo Fp 30 mcg and 50 mcg with respect to lung function in patients 4-11 years of age. The co-primary endpoint results were supported by multiple secondary endpoints, strengthening our ability to rely on the evidence presented in this trial. No new safety signals were noted. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments and recommendation of approval for sNDA 208798-S08. The submitted clinical program is adequate to support the efficacy and safety of Fp 30 mcg and 50 mcg BID for the treatment of asthma in patients 4-11 years of age. The Agency and Applicant have also agreed upon final labeling language for Fp. The action for this application (sNDA 208798-S08) will be ***Approval.***

15 Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

From Trial 30003, the Applicant certified the absence of financial arrangements for 489 of the primary and sub-investigators. In Trial 30003, there was one clinical investigator, Dr. (b) (6), with significant payment of other sorts. Dr. (b) (6) disclosed receiving $31,000 for Teva speaking engagements. There were (b) (6) patients enrolled on Trial 30003 from Dr (b) (6)'s site. Dr. (b) (6) was not involved in evaluating endpoints. This significant payment of other sorts was determined not to have a significant impact upon the conduct of this trial. Removal of these patients would not have affected the interpretation of efficacy and safety.

Covered Clinical Study (Name and/or Number): FSS-AS-30003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 490		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1 Summary of Bioanalytical Assays

Fp and salmeterol concentrations in human plasma samples from Study FSS-PK-10007 in pediatric patients with asthma were simultaneously determined using a validated liquid chromatography-tandem mass spectrometry method (Validation report P1197, (b) (4)) (Table 28). The bioanalytical assays for measuring Fp and salmeterol plasma concentrations were generally acceptable. All 405 clinical samples were analyzed the established stability period at -25±5°C (554 days for Fp and 249 days for salmeterol) (Bioanalytical report DP-2016-133).

Table 28. Summary of Bioanalytical Method Performance of P1197.02

Bioanalytical method validation report name, amendments, and hyperlinks	P1197, which includes 1 initial validation report and 6 addendums.
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. The final extract is analyzed via UPLC with MS/MS detection using positive ion electrospray. Precursor→product ion is 501.1→313.1 for fluticasone propionate, 506.1→313.1 for fluticasone propionate-d_5, 416.2→232.2 for salmeterol, and 419.2→235.2 for salmeterol-d_3.
Materials used for standard calibration curve and concentration	• Fluticasone propionate: 0.500, 1.00, 1.50, 5.00, 20.0, 60.0, 160, and 200 pg/mL • Salmeterol: 0.500, 1.00, 1.50, 5.00, 20.0, 60.0, 160, and 200 pg/mL
Validated assay range	• Fluticasone propionate: 0.500 to 200 pg/mL • Salmeterol: 0.500 to 200 pg/mL
Materials used for quality controls (QCs) and concentration	• Fluticasone propionate: 0.500, 1.20, 3.00, 10.0, 35.0, and 150 pg/mL • Salmeterol: 0.500, 1.20, 3.00, 10.0, 35.0, and 150 pg/mL
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	• Fluticasone propionate: USP[a], Lot # G0K029 and Lot # H0L509 • Fluticasone Propionate-d_5 (IS): BDG[a], Lot # BDG 2425.3 • Salmeterol xinafoate: USP[a], Lot # F0I185 • Salmeterol-d_3 (IS): CDN[a], Lot # K118P8
Regression model and weighting	• Fluticasone propionate: 1/concentration^2 • Salmeterol: 1/concentration

Validation parameters	**Method validation summary**			**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	Fluticasone propionate	8	P1197, Table 2A
		Salmeterol	8	P1197 Addendum 6, Table 2
	Cumulative accuracy (%RE[b]) from LLOQ to ULOQ	Fluticasone propionate	-1.19% to 1.77%	P1197, Table 2A
		Salmeterol	-1.28% to 1.24%	P1197 Addendum 6, Table 2
	Cumulative precision (%CV) from LLOQ to ULOQ	Fluticasone propionate	1.94% to 3.42%	P1197, Table 2A
		Salmeterol	1.65% to 8.26%	P1197 Addendum 6, Table 2
Performance of QCs during accuracy and precision runs	Intra-assay accuracy (%RE[b])	Fluticasone propionate	-6.19% to 5.43%	P1197, Tables 4A-1 through 4A-3
		Salmeterol	-13.3% to 17.0%	P1197 Addendum 6, Tables 3A through 3D
	Intra-assay precision (%CV)	Fluticasone propionate	1.19% to 12.2%	P1197, Tables 4A-1 through 4A-3
		Salmeterol	0.723% to 24.0%	P1197 Addendum 6, Tables 3A through 3D
	Inter-assay accuracy (%RE[b])	Fluticasone propionate	-1.95% to 1.55%	P1197, Table 5A
		Salmeterol	-3.57% to 2.23%	P1197 Addendum 6, Table 4
	Inter-assay precision (%CV)	Fluticasone propionate	1.74% to 9.39%	P1197, Table 5A
		Salmeterol	2.49% to 17.6%	P1197 Addendum 6, Table 4
	Total error (TE)	Not applicable		

Selectivity and matrix effect	No significant interfering peaks noted in blank plasma samples; Matrix factor results were deemed acceptable	P1197, Tables 20A-1 and 20A-2 and P1197 Addendum 6, Table 12; P1197, Tables 19A-1 through 19A-4 and P1197 Addendum 6, Tables 11A through 11D
Interference and specificity	No significant interfering peaks noted at the mass transitions and expected retention times of the analytes or IS; No significant matrix suppression effects that could compromise the sensitivity or accuracy; Non-interference with azelastine and desmethylazelastine (fluticasone propionate only); No effect on the quantitation of fluticasone propionate and salmeterol fortified to mometasone furoate	P1197, Tables 18A-1, 20A-1, and 20A-2 and P1197 Addendum 6, Tables 10A and 12; P1197, Table 18A-2 and P1197 Addendum 6, Table 10B; P1197 Addendum 2, Table 3A; P1197 Addendum 4, Tables 1A and 1B
Hemolysis effect	No effect from hemolysis on the quantitation of fluticasone propionate and salmeterol	P1197, Table 16A and P1197 Addendum 6, Table 8
Lipemic effect	No effect from lipemia on the quantitation of fluticasone propionate and salmeterol	P1197, Table 17A and P1197 Addendum 6, Table 9A
Dilution linearity	10.0 pg/mL diluted 2-fold; 500 pg/mL diluted 5-fold	P1197, Table 6A and P1197 Addendum 6, Table 6
Bench-top/process stability	21.16 hours to thaw and remain at room temperature (fluticasone propionate only); Post-preparative extract stability at 2°C to 8°C were 115.5 hours for fluticasone propionate and 101.25 hours for salmeterol	P1197 Addendum 5, Table 2; P1197, Tables 11A and 11B
Freeze-thaw stability	4 cycles thawed at room temperature from -20°C in matrix with azelastine and desmethylazelastine (fluticasone propionate only); 3 cycles thawed at room temperature from -20°C (fluticasone propionate only)	P1197 Addendum 2, Tables 1A-1 and 1A-2; P1197 Addendum 5, Table 1

Validation parameters	Method validation summary	Source location
Long-term storage	249 days at -20°C and -70°C (fluticasone propionate and salmeterol); 159 days at -20°C in frozen matrix with azelastine and desmethylazelastine (fluticasone propionate only); 554 days at -20°C (fluticasone propionate only)	P1197 Addendum 2, Tables 2A-1, 2A-3, 4A-1, and 4A-2; P1197 Addendum 3, Table 1; P1197 Addendum 5, Table 3
Parallelism	Not applicable	
Carryover	≤20.0% of LLOQ peak for fluticasone propionate; for salmeterol, >20% of the LLOQ in the first carryover blank, and therefore must be continually monitored on a set-by-set basis[c]	P1197, Section of Carryover
Method performance in Study FSS-PK-10007 (DP-2016-133)		
Validation parameters	**Method validation summary**	**Source location**
Assay passing rate	100% for both fluticasone propionate and salmeterol	DP-2016-133, Tables 6A and 8B
Standard curve performance[a]	%RE[b]: -1.8% to 1.5% for fluticasone propionate and -3.5% to 3.4% for salmeterol %CV: 3.5% to 6.1% for fluticasone propionate and 4.1% to 11.1% for salmeterol	DP-2016-133, Tables 4A and 5B
QC performance[a]	%RE[b]: 1.8% to 5.5% for fluticasone propionate and 6.6% to 10.4% for salmeterol %CV: 5.1% to 10.9% for fluticasone propionate and 5.0% to 7.1% for salmeterol	DP-2016-133, Tables 5A and 6B
Method reproducibility	47 (out of 405) of the study samples were reassayed. The results of the incurred sample repeats (100% pass for both fluticasone propionate and salmeterol) met the acceptance criteria (ie, two-thirds of the repeated samples had a relative percent difference of ≤20%)	DP-2016-133, Tables 6A and 8B
Study sample analysis/stability	All samples were received frozen. All samples were analyzed within the 554 days for fluticasone propionate and 249 days for salmeterol demonstrated long-term storage stability in human plasma containing potassium oxalate/sodium fluoride at -25°C±5°C.	DP-2016-133, sections of Sample Receipt and Sample Analysis
Standard calibration curve performance during accuracy and precision runs	Not applicable	

Source: Table 3 of of Appendix B, Summary of Biopharmaceutic Studies and Associated Analytical Methods, page 13-16
The reported intra-assay accuracy and precision for salmeterol were from 4 validation runs: 1AHCH6, 2AHCH6, 3AHCH6, and 4AHCH6. In Run 3AHCH6, the IA 0 samples (0.5 pg/mL, LLOQ) did not meet the acceptance criteria due to the %CV (24.0%) exceeding 20% with the blanks also exceeded 20% of the LLOQ for salmeterol. As a result, an additional run (4AHCH6) was analyzed. In all other 3 runs, all QC samples met the acceptance criteria (≤15%, and ≤20% for LLOQ . Therefore, the intra-assay accuracy and precision for salmeterol are acceptable.
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; MRD, minimum required dilution; MS, mass spectrometry; RE, relative error; QC, quality control; TE, total error; ULOQ, upper limit of quantification; UPLC, ultra performance liquid chromatrography

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT H LIM
07/09/2021 11:11:24 AM

BANU A KARIMI SHAH
07/09/2021 11:12:44 AM