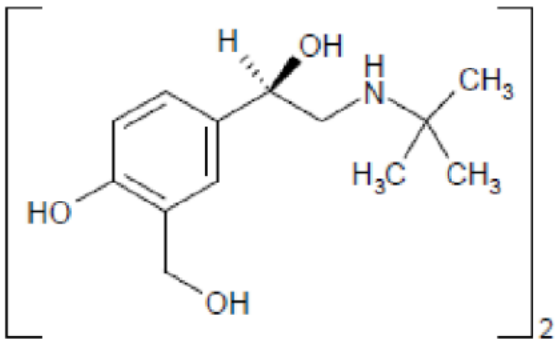
CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	205636 SDN73; Supplement Number - 004
Submissions Date:	06/29/2015
Submission Type:	Efficacy Supplement
Proposed Brand Name:	ProAir RespiClick
Generic Name:	Albuterol Sulfate
Sponsor:	TEVA Pharmaceuticals
Route of Administration:	Inhalation
Dosage Form:	Multi-Dose Dry Powder Inhaler
Dosage Strength:	108 µg albuterol sulfate (equivalent to 90 µg albuterol) per actuation
Proposed Dosing Regimen:	• Treatment or prevention of bronchospasm in adults and children age 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient. • Prevention of exercise-induced bronchospasm in adults and children age 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise.
Proposed Indication(s):	• Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. • Prevention of exercise-induced bronchospasm in patients 4 years of age and older.
Proposed Population(s):	Patients 4 years of age and older
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Suresh Doddapaneni Ph.D.
Molecular Structure:	 H_2SO_4 and enantiomer

Note –
For reviews of individual studies, early development names Albuterol MDPI sometimes are used to refer to the FDA-granted proprietary name ProAir RespiClick.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

ProAir RespiClick® was originally approved on 3/31/2015. The original approved patient population was 12 years of age and older. In this supplement, ProAir RespiClick® is proposed to treat the patient population with the same indications, but aged 4 years and older. The indications are:

1) Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease;
2) Prevention of exercise-induced bronchospasm in patients 4 years of age and older.

The proposed dosing regimens are:

1) Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.
2) Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise.

The dosage form is an inhalation powder and each metered dose delivers 108 µg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base). The inhaler is supplied as a 0.65g single unit containing 200 inhalations.

In this efficacy supplement, Teva relied on its own approved product, NDA 021457 ProAir HFA, as a reference product for the purpose of PK and PD comparisons in two clinical pharmacology studies. The dosing regimen of ProAir RespiClick is the same as ProAir HFA.

Two clinical pharmacology studies were submitted under this supplement:

Study ABS-AS-102 was a Phase 1, single-center, randomized, open-label, single-dose, 2-period, crossover study in 15 pediatric patients aged 6 to 11 years with persistent asthma. The primary objective of the study was PK and PD (vital signs) comparison of ProAir RespiClick and ProAir HFA after administration of a single inhaled dose of 180 µg albuterol. Overall ProAir RespiClick and ProAir HFA had comparable PK and PD profiles.

Study ABS-AS-202 was a Phase 2, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 5-treatment, 5-period, 10-sequence, 5-way crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in 61 children (4 to 11 years of age) with persistent asthma. The patients received each of the following single-dose treatment in each period: placebo, ProAir RespiClick 90 µg, ProAir RespiClick 180 µg, ProAir HFA 90 µg, or ProAir HFA 180 µg. All four active treatments were significantly superior to placebo in improving PPFEV1 AUC_{0-6} and FEV1 AUC_{0-6}. The improvements were comparable between two products. There was no significant difference on improvements between 90 µg or 180 µg delivered by ProAir RespiClick.

1.1 Recommendation

From the perspective of the Office of Clinical Pharmacology, Supplement 004 to NDA 205636 submitted on June 29, 2015 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

ProAir RespiClick® was originally approved on 3/31/2015. The original approved patient population was 12 years of age and older. In this supplement, ProAir RespiClick® is proposed to treat the patient population with the same indications, but aged 4 years and older.

An initial pediatric study plan containing Studies 102, 202, and 303 was submitted on 11/12/2013 under IND 104532. A written response was issued on 02/06/2014 in which the Agency agreed iPSP:

1. We acknowledge that you will request a partial waiver for pediatric patients less than 4 years of age.
2. We acknowledge that you will request a deferral of pediatric studies in children 4 to less than 12 years of age until late 2015.
3. We acknowledge that studies in children 12 years of age and older have been completed and the application is expected to be submitted in 2014.

An agreed pediatric study plan was submitted on 4/10/2014 and the Agency issued an agreement on 05/09/2014.

1.3.2 Albuterol Systemic Exposure Comparison between ProAir RespiClick and ProAir HFA

In Study ABS-AS-102, the geometric mean AUC_{0-t} (measured up to 10 hours) of albuterol in pediatric population was comparable between two products with1663 (N=13, CV = 35%) pg·h/mL for Albuterol MDPI and 1651 (N=13, CV = 30%) for ProAir HFA following single-dose 180 µg inhalation (Figure 1.1). The geometric mean C_{max} of Albuterol MDPI was numerically (27%) higher than that of ProAir HFA, which is consistent with the results obtained from adult Study ABS-AS-101. The median t_{max} of albuterol were 1.0 hour and 2.0 hour for Albuterol MDPI and ProAir HFA, respectively. However the t_{max} may not be precisely measured as there was only one PK sampling point within one hour post-dose.

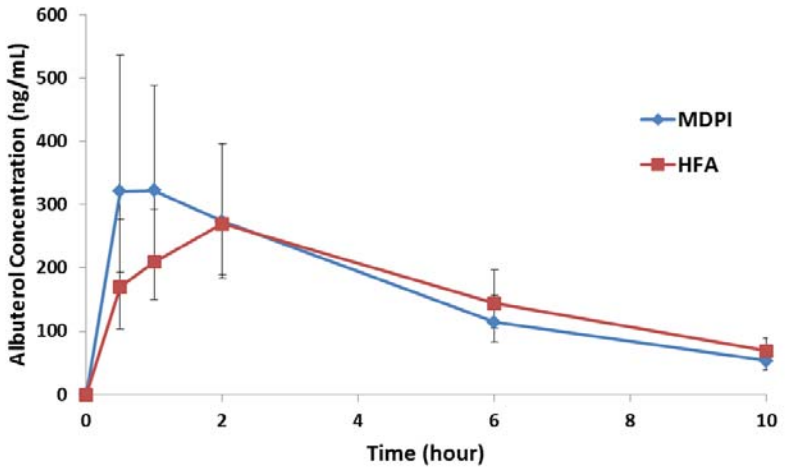


Figure 1.1 Geometric mean plasma concentration-time profiles (PK set) of albuterol following single-dose (180 µg) inhalation via Albuterol MDPI (blue, N=13) or ProAir HFA (red, N=13). (Source: Figure 4.5)

1.3.3 Comparison of vital signs changes between ProAir RespiClick and ProAir HFA

The effect of albuterol on vital signs changes within 6-hour post-dose following single-dose 180 µg inhalation via Albuterol MDPI or ProAir HFA was summarized in Table 1.1. Generally the post-dose maximum mean changes from baseline of systolic blood pressure, diastolic blood pressure and pulse rate were comparable between two treatments.

Table 1.1 Statistical Summary for Maximum Changes of Vital Signs from Baseline following 180 µg Albuterol Single-Dose Treatment in Study ABS-AS-101

Maximum Change of Vital Signs	ProAir RespiClick*	ProAir HFA*
Patient N	15	15
Systolic Blood Pressure (mmHg)	4.5 (1.9)	5.1 (2.0)
Diastolic Blood Pressure (mmHg)	-6.6 (1.2)	-6.1 (1.7)
Pulse Rate (bpm)	10.9 (1.5)	9.1 (2.6)

*** Arithmetic mean (SE)**
Source: Table 4.4

1.3.4 Comparison of bronchodilatory effect following single dose inhalation of ProAir RespiClick or ProAir HFA

The bronchodilatory effect following four single-dose active treatments were compared in asthmatic children 4-11 years in a placebo-controlled, crossover Study ABS-AS-202. The five treatments were:

- Placebo
- 90 µg albuterol via ProAir RespiClick
- 180 µg albuterol via ProAir RespiClick
- 90 µg albuterol via ProAir HFA
- 180 µg albuterol via ProAir HFA

The mean baseline-adjusted FEV1 $AUEC_{0-6}$ for each of the four active treatments was significantly greater than that of placebo ($p<0.0001$) (Table 4.10). The baseline-adjusted peak FEV1 over 6 hours post-dose for each of the four active treatments increased 0.26 to 0.29 L greater than the placebo, indicating a significant bronchodilation effect for both products (Table 4.11). The FEV1 time profile was similar for all four treatments (Figure 1.2). There was no significant difference on FEV1 AUC_{0-6} improvement between two dosing levels (90 µg and 180 µg) of Albuterol MDPI ($p=0.6342$), whereas ProAir HFA 180 µg was superior to ProAir HFA 90 µg ($p=0.0488$) on FEV1 AUC_{0-6} improvement.

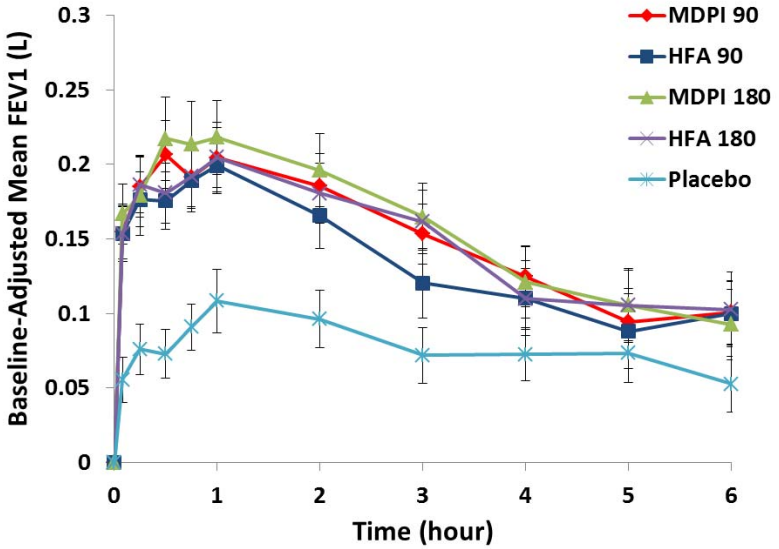


Figure 1.2 Arithmetic baseline-adjusted mean FEV1 following single-dose albuterol delivered as Albuterol MDPI 90 µg (red, N=61), Albuterol MDPI 180 µg (green, N=61), ProAir HFA 90 µg (blue), ProAir HFA 180 µg (purple, N=61), and placebo (cyan, N=61), respectively. Error bars represent the standard error. (Source: Figure 4.8)

The percentage of responders (subjects achieving at least a 15% increase in FEV1 from baseline) was numerically higher following ProAir RespiClick treatment than ProAir HFA treatment at both 90 µg and 180 µg dosing levels (Table 1.2). The median time to onset (15% or greater increase in FEV1 from baseline) was 8 to 9 minutes for active treatments. The median time to peak FEV1 was 46 to 48 minutes for active treatments. The mean duration of response (period between onset and offset of a 15% or greater increase in FEV1) was similar between four treatments, ranging from 2.4 hours to 2.8 hours.

Table 1.2 Comparison of Time-related Endpoints between ProAir RespiClick and ProAir HFA Following Inhalation of Single Dose Albuterol in Study ABS-AS-202

	Treatment		Responder N (%)[1]	Time to Response (min)[2]	Time to Peak FEV1 (min)[2]	Duration of Response (hour)[3]
Pediatric Study 202	90 µg	RespiClick	26/61 (44.8%)	8.8 (4.8, 18.5)	46.9 (3.1, 364.7)	2.8 (2.37)
		HFA	22/61(37.3%)	8.4 (4.0, 26.6)	48.3 (4.1, 358.5)	2.4 (2.21)
	180 µg	RespiClick	27/61 (45.8%)	8.0 (4.7, 29.7)	46.1 (5.0, 360.1)	3.0 (2.29)
		HFA	24/61 (40.7%)	8.4 (4.2, 28.7)	48.1 (4.2, 310)	2.8 (2.48)
	Placebo		10/61 (17.0%)	-	64.6 (4.6, 359.4)	-
Approved NDA 205636 label	180 µg RespiClick		44/78 (56.4%)	5.7	-	~ 2

[1] number of responders with at least 15% increase from baseline FEV1 within 30 min post-dose.
[2] median (range)
[3] mean (SD)
Source: reviewer's summary from Table 4.13, 4.14, 4.15, and 4.16; CSR 202, page 163, Summary 15.2.21.1)

2. QUESTION BASED REVIEW

2.1 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the sNDA

In total three pediatric studies were submitted under this sNDA: Study ABS-AS-102 (Study102), Study ABS-AS-202 (Study 202), and Study ABS-AS-303 (Study 303). Among them, Study 102 was a Phase 1 PK study; Study 202 was a Phase 2 dose-ranging PD Study; Study 303 was a Phase 3 efficacy and safety Study.

Table 2.1 List of Five Clinical Pharmacology Studies in sNDA205636 Pediatric Submission Package

Study ID	Study Date	Phase	Study Objectives	Study Design	Subjects	Treatments
ABS-AS-102	05/04/2013 – 07/10/2013	1	PK, PD, safety	R, OL, SD, 2-Period CO	15 children (6-11yo) with persistent asthma	ProAir RespiClick 180 µg ProAir HFA 180 µg
ABS-AS-202	07/11/2013 – 10/09/2013	2	PD/efficacy, safety	R, DB, DD, PC, 5-Period CO	61 children (4-11yo) with persistent asthma	ProAir RespiClick 90 µg ProAir RespiClick 180 µg ProAir HFA 90 µg ProAir HFA 180 µg Placebo

R=randomized, OL=open label, SD=single dose, CO=cross over, DB=double blind, DD=double dummy, PC=placebo-controlled.
Source: section 5.2, pediatric tabular listing of all clinical studies

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

The drug substance, albuterol sulfate is a racemic salt of albuterol with the chemical name α1-[(*tert*-butylamino) methyl]-4-hydroxy-*m*-xylene- α, α1-diol sulfate (2:1) (salt). Albuterol sulfate is a white to off-white crystalline powder. It is soluble in water and slightly soluble in ethanol.

Table 2.2 outlines the quantities of each active ingredient and excipient per container. Each container has (b) (4) 200 doses. Each actuation delivers 108 µg albuterol sulfate (equivalent to 90 µg albuterol) with (b) (4) lactose monohydrate (b) (4).

Table 2.2 Ingredients and Their Quantities per Albuterol MDPI Inhaler Container

Ingredients	Quantity
Albuterol sulfate	(b) (4)
Lactose monohydrate	
Target fill weight per device	
Fraction of drug substance (%w/w)	

Source: Section 3.2.P.1 Page 1, Table 1

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

Beta2-adrenergic receptor is a G_s-protein-coupled receptor expressed on the surface of bronchial smooth myocytes. Upon binding with ligand such as epinephrine, the receptor triggers activation of adenylcyclase and to an increase in the intracellular concentration of cAMP. This increase of cAMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol is a selective beta2-adrenergic receptor agonist with selectivity binding ratio (β2/β1) of 1375[1].

The proposed therapeutic indications of ProAir RespiClick are:

- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older.

2.2.3 What are the proposed dosage(s) and route(s) of administration?

ProAir RespiClick is for oral inhalation only. The proposed dosages are:

- Treatment or prevention of bronchospasm in adults and adolescents age 4 and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.
- Prevention of exercise-induced bronchospasm in adults and adolescents age 4 and over: 2 inhalations 15 to 30 minutes before exercise.

2.3 General Clinical Pharmacology

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

PK parameters (AUC_{0-t} and C_{max} as primary endpoints; AUC_{0-inf}, tmax, and $t_{1/2}$ as secondary endpoints) and vital signs changes were the major endpoints for Study ABS-AS-102.

Post-dose PPFEV1 AUC_{0-6} and FEV1 AUC_{0-6} were the primary and secondary efficacy endpoints for Study ABS-AS-202. These spirometry endpoints directly measuring the pulmonary ventilation function and bronchodilatory effect following the treatments

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

The parent compound, albuterol, is the active moiety. Plasma concentrations of racemic albuterol were measured using a validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) method.! The concentrations of (R) - and (S) - enantiomers of albuterol were not measured separately.

2.4 PK Characteristics of the Drug

2.4.1 How is the systemic exposure in children compared to that in adults?

The systemic exposure following single-dose 180 µg ProAir RespiClick inhalation in children 6-11 years of age (N=13) was similar to that in adults. The difference in C_{max}, AUC_{0-t}, and AUC_{0-inf} were all less than 10% (Table 2.3).

Table 2.3 Geometric Mean (CV%) of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Children and Adults

PK parameters	Children	Adults	Ratio (Children/Adults)
Study	Study 102	Study 304	
Patient N	13	16	-
AUC_{0-t} (pg*h/mL)	1663 (35%)	1620 (39%)	1.03
C_{max} (pg/mL)	353 (43%)	325 (38%)	1.09
AUC_{0-inf} (pg*h/mL)	1953 (32%)	2147 (36%)	0.91
T_{max} (hour)*	1.0 (0.5, 2.0)	0.475 (0.18 - 4.95)	-
$T_{1/2}$ (hour)	3.5 (25%)	4.51 (34%)	-

Source: Table 4.2 from this review and Table 4.46 in Clinical Pharmacology Review of NDA 205636 dated on 01/27/2015

2.4.2 What are the characteristics of drug absorption?

The median t_{max} in children was 1.0 hour whereas 0.5 hour in adults (Table 2.3). The difference was more likely contributed by different PK sampling scheme in adults and children. There were two post-dose time points within 1 hour (15 min and 30 min) in adult Study 304 and only as one post-dose time point in pediatric Study 102 (30 min).

2.4.3 What are the characteristics of drug distribution?

The volume of distribution of albuterol in pediatric population was not estimated by the sponsor.

2.4.4 What are the characteristics of drug metabolism?

Referring to the approved label of NDA 205636 ProAir RespiClick dated on 03/31/2015, "the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)- albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3."

2.4.5 What are the characteristics of drug elimination?

Referring to the approved label of NDA 205636 ProAir RespiClick dated on 03/31/2015, "The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine."

2.5 Intrinsic Factors

2.5.1 Does body weight, gender, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Body weight (Figure 2.1), age (Figure 2.2), sex (Figure 2.3), and race (Figure 2.4) do not significantly change the AUC_{0-t} and C_{max} of Albuterol in pediatric population (PK set N=13) from Study 102.

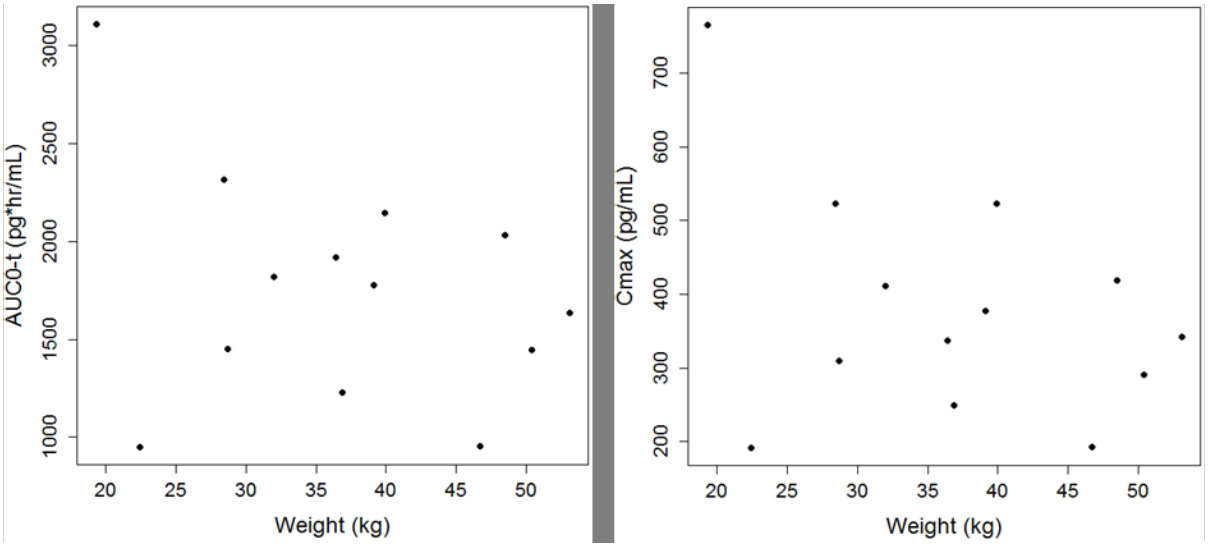


Figure 2.1 Scatter plot of subjects' body weight (N=13) and their AUC_{0-t} (left panel, p=0.28) and C_{max} (right panel, p=0.20) following single-dose inhalation of 180 µg albuterol via ProAir RespiClick (Reviewer's analysis).

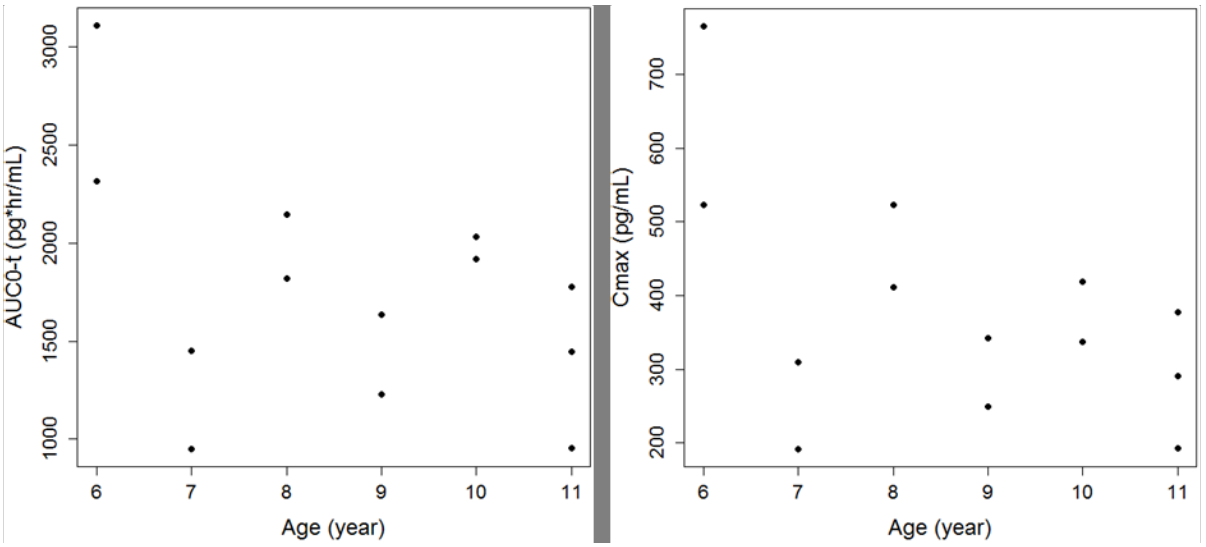


Figure 2.2 Scatter plot of subjects' age (N=13) and their AUC_{0-t} (left panel, p=0.13) and C_{max} (right panel, p=0.07) following single-dose inhalation of 180 µg albuterol via ProAir RespiClick (Reviewer's analysis).

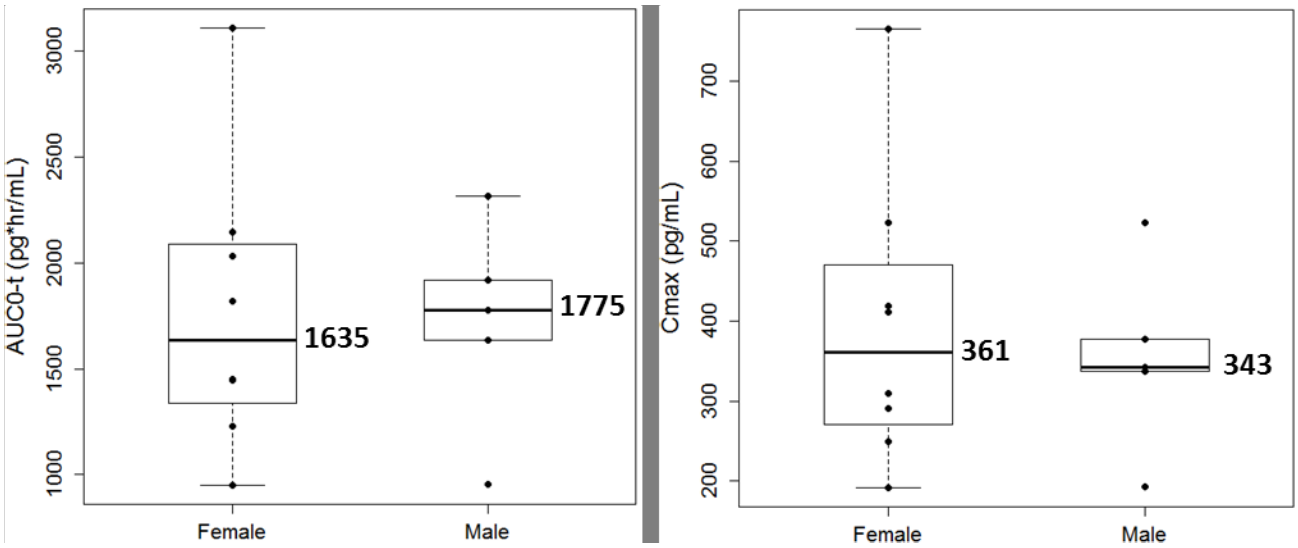


Figure 2.3 Box plot of gender's effect (Female=8, Male=5) on pediatric AUC_{0-t} (left panel, p=0.88) and C_{max} (right panel, p=0.64) following single-dose inhalation of 180 µg albuterol via ProAir RespiClick (Reviewer's analysis).

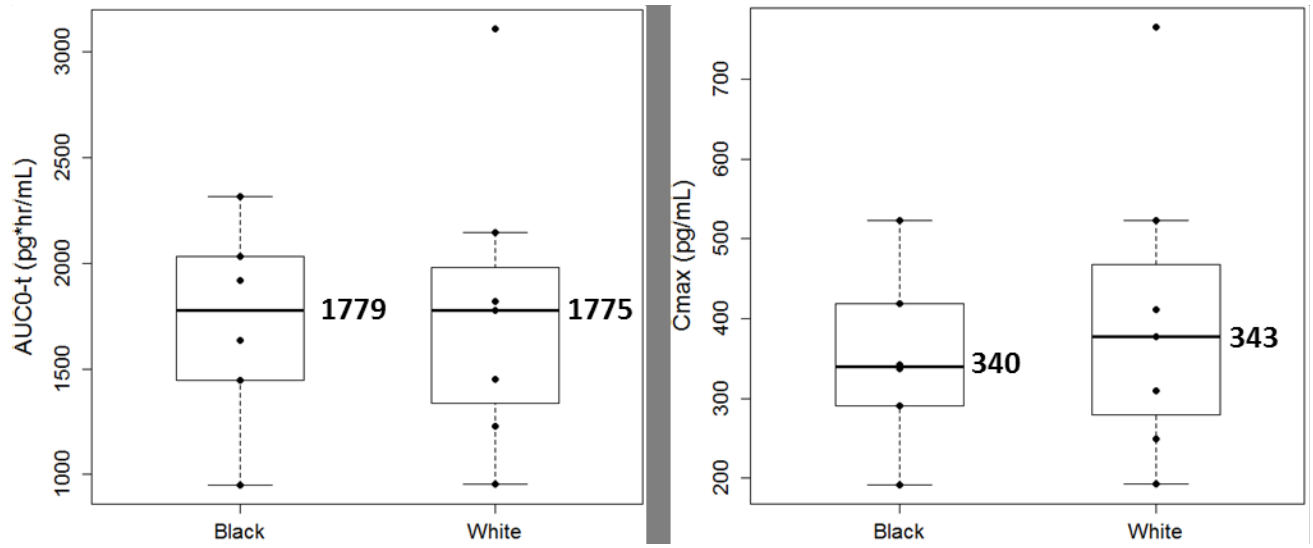


Figure 2.4 Box plot of race' effect (Female=8, Male=5) on pediatric AUC_{0-t} (left panel, p=0.85) and C_{max} (right panel, p=0.55) following single-dose inhalation of 180 µg albuterol via ProAir RespiClick (Reviewer's analysis).

2.5.2 Renal Impairment

Not Applicable

2.5.3 Hepatic Impairment

Not Applicable

2.6 Extrinsic Factors

2.6.1 What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Not Applicable

2.6.2 Drug-drug interactions (DDI)

Not Applicable

2.7 General Biopharmaceutics

2.7.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not Applicable

2.7.2 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

All three pediatric studies utilized the same formulation and inhalation device (NB8) that was approved in adults and adolescents (NDA 205636 approved on 03/31/2015).

2.7.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Not Applicable

2.8 Analytical Section

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

Plasma concentrations of the parent drug, racemic albuterol were measured using a validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) method.!!

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

Due to the nature of the measuring method, it's the total amount of racemic albuterol that was measured.

2.8.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

The range of calibration curves is 2.00 pg/mL to 1000 pg/mL. The lower limit of quantitation was 2.00 pg/ml. The precision and accuracy of low, medium and high quality controls were all within ±15% of the nominal value (Table 2.4). There was no obvious interference from the blank matrix (tested 6 lots) or

among the analyte and internal standard. The results show that this method has sufficient specificity and selectivity. The dilution QCs (5×) met the acceptance criteria which the mean of the calculated concentrations of albuterol were within ≤15.0% of the nominal value. Albuterol was stable in human plasma when kept at approximately 4 °C for 18 hours. Albuterol in human plasma was stable for 279 days at -70 °C. Albuterol in human plasma was stable when subjected to three freeze/thaw cycles.

Table 2.4 Summary of Assay Performance of Albuterol Quality Control for Study ABS-AS-102

Run Date	Curve Number	QCL 6.0 pg/mL	%RE	QCM 400.0 pg/mL	%RE	QCH 800.0 pg/mL	%RE
08-Aug-2013	1	5.8	-3.33	393.3	-1.68	827.7	3.46
		6.0	0.00	385.5	-3.63	764.6	-4.43
09-Aug-2013	2	6.2	3.33	389.0	-2.75	793.6	-0.80
		6.5	8.33	387.2	-3.20	791.9	-1.01
09-Aug-2013	3	6.0	0.00	424.9	6.23	844.3	5.54
		5.8	-3.33	393.4	-1.65	810.7	1.34
14-Aug-2013	4	6.5	8.33	385.4	-3.65	753.9	-5.76
		5.8	-3.33	393.5	-1.63	768.4	-3.95
Mean		6.1		394.0		794.4	
S.D.		0.3		12.9		31.8	
%CV		4.92		3.27		4.00	
%RE		1.67		-1.50		-0.70	
n		8		8		8	

Source: section 5.3.4.2 bioanalytical report, page 24, Table 4

3 DETAILED LABELING RECOMMENDATIONS

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albuterol sulfate is a beta$_2$-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta$_2$-adrenergic receptors on airway smooth muscle. Activation of beta$_2$-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta$_2$-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [*see Warnings and Precautions (5.4)]*.

12.2 Pharmacodynamics

In a pharmacodynamic (PD) trial conducted in 47 patients, the PD and safety profiles were similar for PROAIR RESPICLICK and ProAir HFA. Comparable changes from baseline in the PD measures (serum glucose and potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure) were observed following cumulative dose administration up to 1440 mcg of both PROAIR RESPICLICK and ProAir HFA. The overall safety, efficacy and PD profile of PROAIR RESPICLICK and ProAir HFA were comparable.

(b) (4) PROAIR RESPICLICK (b) (4) was significantly greater than placebo and comparable to that of ProAir HFA (b) (4).

Cardiac Electrophysiology

As with other beta$_2$-adrenergic agonists, PROAIR RESPICLICK prolonged QT intervals following a 1440 mcg cumulative dose. The prolongation was comparable to that of ProAir HFA.

12.3 Pharmacokinetics

Absorption

Albuterol was rapidly absorbed into the systemic circulation with peak plasma concentrations occurring at half an hour following single- or multiple-dose oral inhalation(s) of PROAIR RESPICLICK. In a cumulative dose study, the AUC_{0-t} was comparable between PROAIR RESPICLICK group and ProAir HFA group; C_{max} value was approximately one-third higher in PROAIR RESPICLICK group than ProAir HFA group.

Distribution

The volume of distribution has not been determined for PROAIR RESPICLICK. Published literature suggests that albuterol exhibits low *in vitro* plasma protein binding (10%).

Elimination

The accumulation ratio (~1.6 fold) was observed following one week QID dosing. The corresponding effective half-life was approximately 5 hours, which was consistent with the elimination half-life following both single- or multiple-dose administration.

Metabolism

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

Excretion

The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Specific Populations

Age: No pharmacokinetic studies for PROAIR RESPICLICK have been conducted in neonates or elderly subjects. The systemic exposure in children 6 to 11 years of age is similar to that of adults following 180 mcg single dose inhalation of PROAIR RESPICLICK.

Sex: The influence of sex on the pharmacokinetics of PROAIR RESPICLICK has not been studied.

Race: The influence of race on the pharmacokinetics of PROAIR RESPICLICK has not been studied.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of PROAIR RESPICLICK to patients with renal impairment *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of PROAIR RESPICLICK has not been evaluated.

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

4. Appendix

4.1 Appendix – Individual Study Review

Note –
For reviews of individual studies, early development names Albuterol MDPI sometimes are used to refer to the FDA-granted proprietary name ProAir RespiClick.

4.1.1 Study ABS-AS-102 (Study 102)

Study Type: Phase 1 PK, PD, and safety single-dose crossover study in asthma children (6 to 11 years)

Title: Comparison of the Pharmacokinetic and Pharmacodynamic Profiles of Albuterol Spiromax and ProAir HFA in Pediatric Patients with Persistent Asthma

Objective:
The primary objective of the study was to compare the pharmacokinetic profiles of Albuterol MDPI and ProAir HFA after administration of a single inhaled dose of 180 mcg albuterol base from each product in pediatric patients aged 4-11 years with persistent asthma.

The secondary objective was to compare the PD and safety profiles of Albuterol MDPI and ProAir HFA in pediatric patients.

Study Design and Method:
This investigation was Phase 1, single-center, randomized, open-label, single-dose, 2-period, crossover study in pediatric patients aged 6 to 11 years, inclusive, with persistent asthma. In each period, each child received 180 µg single-dose of albuterol (2 inhalations of 90 µg) delivered either by Albuterol MDPI or ProAir HFA. The washout period between two periods was 4 to 14 days. A total of 15 patients (5 males and 10 females) were enrolled with 14 were included in PK population; however, 13 patients were evaluable for PK in each treatment sequence.

Noteworthy inclusion criteria:

- Male or pre-menarchal female patient 4-11 years of age, inclusive, as of the screening visit.
- Documented physician diagnosis of persistent asthma of a minimum of 3 months duration that was stable for at least 4 weeks prior to the screening visit. The asthma diagnosis was in accordance with the National Asthma Education and Prevention Program (NAEPP).
- FEV1 ≥80% predicted for age, height and sex and race at the SV based on the pediatric population standards.
- Any patient being treated with ICS was on a low-dose regimen (200 µg or less of fluticasone propionate per day or equivalent), which was stable for at least 4 weeks prior to the screening visit and which was expected to be maintained for the duration of the study.
- Required <4 inhalations per week of a rescue bronchodilator (on average) for the 4 weeks preceding the screening visit.

Noteworthy exclusion criteria:

- History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest, or hypoxic seizures.
- Any asthma exacerbation requiring systemic corticosteroids within 3 months of the screening visit or any hospitalization for asthma within 6 months prior to the screening visit.

- Use of any prohibited concomitant non-asthma medications including treatment with β2-adrenergic receptor antagonists and non-selective β-receptor blocking agents like β-blocking anti-hypertensive products (administered by any route), monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, and/or systemic corticosteroids.

During each treatment period, PK samples were collected at pre-dose (5 ± 2 minutes prior to dosing), 30 (±2), 60 (±2), 120 (±2), 360 (±2), and 600 (±2) minutes after completion of dose.

Albuterol PK parameters were estimated using non-compartmental methods. All values below the lower limit of quantitation (BLQ) were considered as zero during the PK and statistical analyses. No concentration estimates were interpolated or predicted for missed concentration time points.

Endpoints:

- PK endpoints:
  - Primary: AUC_{0-t} and C_{max}
  - Secondary: AUC_{0-inf}, tmax, and $t_{1/2}$

- PD endpoints: treatment effects on serial vital signs (blood pressure, pulse rate) over 6 hours postdose. 12-lead electrocardiograph (ECG) and clinical laboratory tests were conducted at the end of treatment visit 2 or at the time of early discontinuation from the study.

Demographics:

A total of 24 patients with persistent asthma were screened for this study. Of the 24 patients screened, 15 patients at 1 center in the US met entry criteria and were considered to be eligible for enrollment into the study. All 9 patients who were not enrolled did not meet entry inclusion criteria. All 15 patients enrolled were included in the safety population. A total of 14 patients were included in the PK population (patient 10538008 missed the blood draw at 30 minutes after dosing with ProAir HFA due to difficulty obtaining blood. This patient also had an albuterol plasma concentration prior to dosing which exceeded 5% of C_{max} during the Albuterol MDPI treatment period). Furthermore, an additional 2 patients (10538012 and 10538013) had data excluded from the PK data set for 1 period each because their albuterol plasma concentrations also exceeded 5% of C_{max} prior to dosing. Therefore, 13 patients in each treatment group were evaluable for PK. The demographic characteristics were listed in Table 4.1.

Table 4.1 Demographic Information (Enrolled/Randomized Analysis Set)

Demographic Variables		Total (N=15)
Age (years)	Mean (SD)	8.6 (1.88)
	Median (range)	9 (6, 11)
Sex	Male (N)	5
	Female (N)	10
Race	White (N)	7
	Black (N)	7
	Other (N)	1
Body Weight (kg)	Mean (SD)	36.3 (10.5)
	Median (range)	36.9 (19.3, 53.1)
Height (cm)	Mean (SD)	137.6 (14.2)
	Median (range)	139.4 (116.4, 157.9)
BMI (kg/m^2)	Mean (SD)	18.7 (2.59)
	Median (range)	18.5 (14.2, 22.8)

Source: adapted from CSR Report 102, page 48, Table 4

PK Results:

The geometric mean AUC_{0-t} (measured up to 10 hours) of albuterol was comparable between two products with1663 (CV = 35%) pg·h/mL for Albuterol MDPI and 1651 (CV = 30%) for ProAir HFA after single-dose inhalation (Table 4.2). The geometric mean C_{max} of Albuterol MDPI was numerically (27%) higher than that of ProAir HFA (Figure 4.1), which is consistent with the results obtained from adult Study ABS-AS-101. The median t_{max} of albuterol were 1.0 hour and 2.0 hour for Albuterol MDPI and ProAir HFA, respectively. However the t_{max} may not be precisely measured as there was only one PK sampling point within one hour post-dose.

Table 4.2 Geometric Mean (CV%) of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Children Aged 6-11 Years Old (PK Set)

PK parameters	Albuterol MDPI	ProAir HFA
Patient N	13	13
AUC_{0-t} (pg·h/mL)	1663 (35%)	1651 (30%)
C_{max} (pg/mL)	353 (41%)	278 (36%)
AUC_{0-inf} (pg·h/mL)	1953 (33%)	2103 (26%)
t_{max} (hour)*	1.0 (0.5, 2.0)	2.0 (1.0, 2.0)
$t_{1/2}$ (hour)	3.5 (23%)	4.2 (27%)

*** Median (range)**

Source: adapted from CSR 102, page 57, Table 7

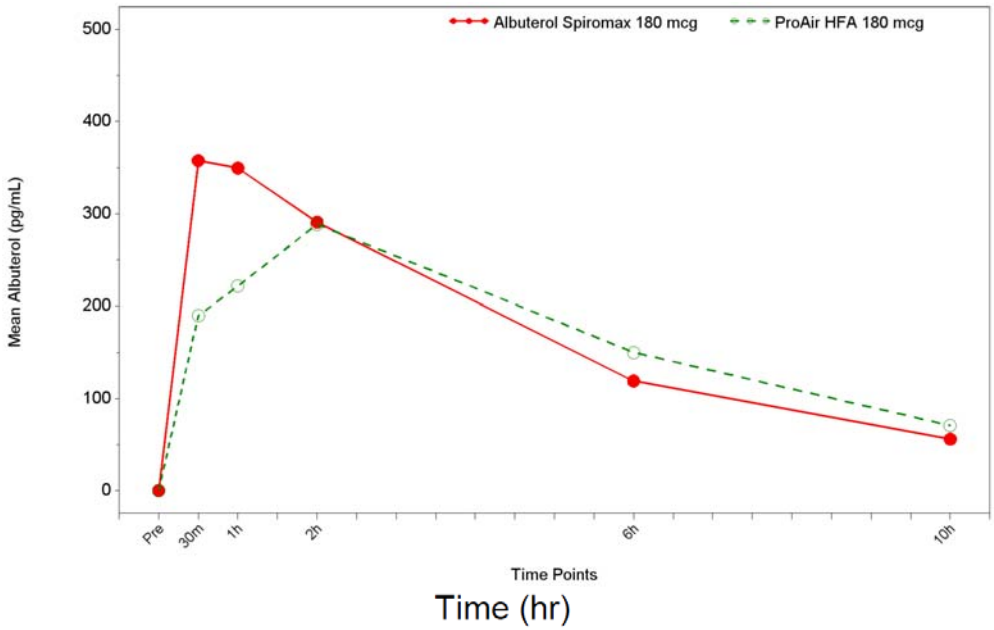


Figure 4.1 Arithmetic mean plasma concentration-time profiles of albuterol following single-dose (180 µg) inhalation via Albuterol MDPI (red, N=13) or ProAir HFA (green, N=13). (Source: CSR Report 102, page 56, Figure 1)

Results of a statistical comparison between 12 subjects whose PK data were available for both treatments showed that the ratios (Albuterol MDPI/ProAir HFA) of AUC_{0-t}, AUC_{0-inf}, and C_{max} were 1.056 (90% CI = 0.880, 1.268), 0.971 (90% CI = 0.821, 1.147), and 1.340 (90% CI = 1.098, 1.636), respectively (Table 4.3).

Table 4.3 Statistical Comparison of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Children Aged 6-11 Years Old

PK parameters	Albuterol MDPI*	ProAir HFA*	Ratio (MDPI/HFA)[#]
Patient N	12	12	
AUC_{0-t} (pg·h/mL)	1705	1614	1.056 (0.88, 1.268)
AUC_{0-inf} (pg·h/mL)	2010	2071	0.971 (0.821, 1.147)
C_{max} (pg/mL)	363	271	1.340 (1.098, 1.636)

*** Least square mean**
[#] Ratio (90% CI)
Source: adapted from CSR 102, page 111, Summary 15.2.4.1

PD Results:

- **Systolic Blood Pressure**

There was an overall, moderate increase in mean systolic blood pressure following administration of both products. The systolic blood pressure remained relative stable and did not return to baseline by the 6-hour post-dose time point in both treatment groups (Figure 4.2). The systolic blood pressure mean changes from baseline were comparable between two products. The difference of maximum increase from baseline between two products was less than 1 mmHg (Table 4.4).

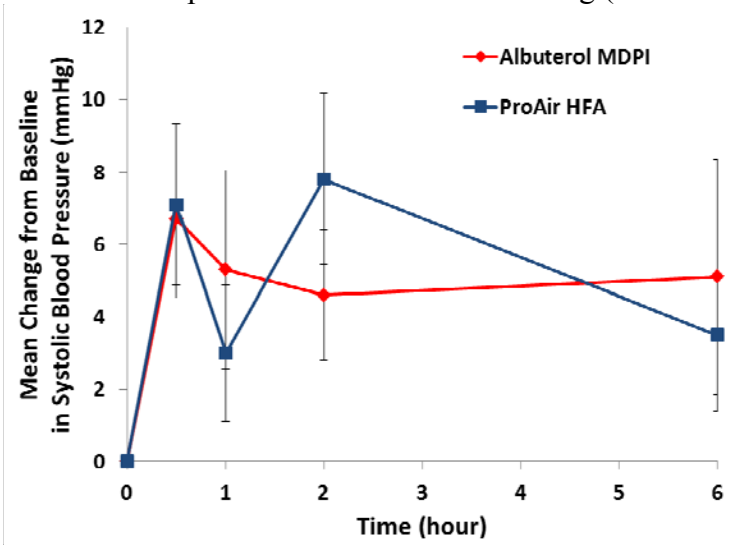


Figure 4.2 Arithmetic mean change from baseline in systolic blood pressure following inhalation of 180 µg albuterol via either Albuterol MDPI (red) or ProAir HFA (blue). Error bars represent the standard error. (Source: adapted from CSR 102, page 182-184, Summary 15.3.16)

Table 4.4 Statistical Summary for Maximum Changes of Vital Signs from Baseline by Treatment

Maximum Change of Vital Signs	Albuterol MDPI*	ProAir HFA*
Patient N	15	15
Systolic Blood Pressure (mmHg)	4.5 (1.9)	5.1 (2.0)
Diastolic Blood Pressure (mmHg)	-6.6 (1.2)	-6.1 (1.7)
Pulse Rate (bpm)	10.9 (1.5)	9.1 (2.6)

*** Arithmetic mean (SE)**
Source: adapted from CSR 102, page 114, Summary 15.2.5.2

- **Diastolic Blood Pressure**

The mean diastolic blood pressure fluctuated around baseline following administration of both products. The mean diastolic blood pressure appeared higher than the baseline at the 6-hour post-dose time point in both treatment groups (Figure 4.3). The diastolic blood pressure mean changes from baseline were comparable between two products. The difference of maximum decrease from baseline between two products was less than 1 mmHg (Table 4.4).

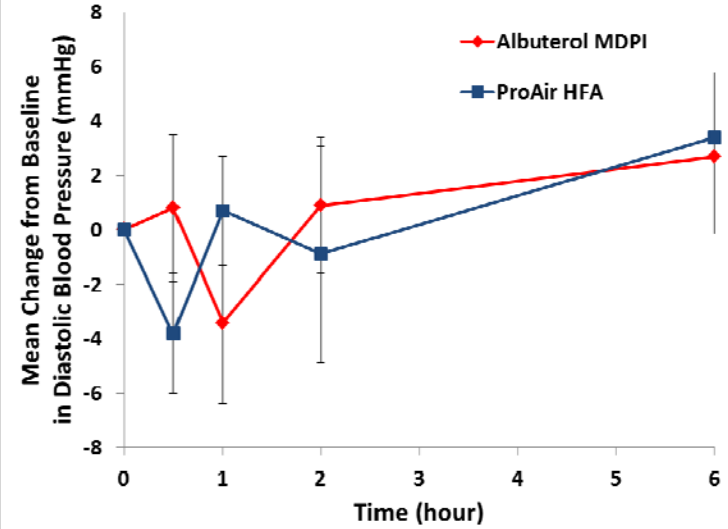


Figure 4.3 Arithmetic mean change from baseline in diastolic blood pressure following inhalation of 180 µg albuterol via either Albuterol MDPI (red) or ProAir HFA (blue). Error bars represent the standard error. (Source: adapted from CSR 102, page 185-187, Summary 15.3.16)

- **Pulse Rate**

There was an overall, decrease in mean pulse rate till 2 hours following administration of both products. The mean pulse rate appeared higher than the baseline at the 6-hour post-dose time point in both treatment groups (Figure 4.4). The pulse rate mean changes from baseline were comparable between two products. The difference of maximum increase from baseline between two products was less than 2 (Table 4.4).

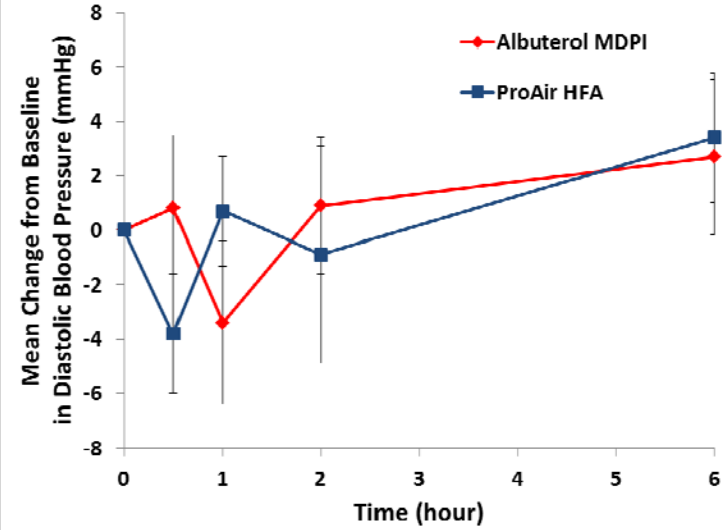


Figure 4.4 Arithmetic mean change from baseline in pulse rate following inhalation of 180 µg albuterol via either Albuterol MDPI (red) or ProAir HFA (blue). Error bars represent the standard error. (Source: adapted from CSR 102, page 188-190, Summary 15.3.16)

- **ECG**

The endpoint ECG variables were measured at baseline and at endpoint. One patient had a shift from normal at baseline to abnormal at endpoint (clinically non-significant abnormal sinus rhythm) and 4 patients were abnormal at baseline. The mean QT, QTcB, and QTcF values at endpoint were all less than those of baseline (Table 4.5). No patient had a QTc interval length (Bazett or Fridericia) greater than 456 msec at any time point.

Table 4.5 Statistical Summary for ECG Variables Changes from Baseline at Endpoint

ECG Variables Change from Baseline	At Endpoint Time*
Patient N	15
Heart Rate (bpm)	1.3 (2.6)
QT Interval (ms)	-5.3 (5.5)
QTcB Interval (ms)	-2.4 (4.3)
QTcF Interval (ms)	-3.3 (3.8)

*** Arithmetic mean (SE)**
Source: adapted from CSR 102, page 192-197, Summary 15.3.18

Safety Results:
There were no treatment-emergent adverse events, deaths, serious adverse events, or discontinuations due to adverse events. No clinically significant changes were seen in laboratory parameters, physical examination findings, vital signs, or electrocardiograms between baseline and endpoint.

Conclusions:
The results of this study demonstrate that Albuterol MDPI and ProAir HFA had comparable PK and PD profiles in pediatric patients following the administration of single inhaled 180 µg albuterol doses.

Systemic exposure to inhaled albuterol following Albuterol MDPI administration was comparable to that of ProAir HFA as based on the analyses of AUCs. Although C_{max} was 27% higher for Albuterol MDPI in this study, the PD and overall safety profiles were similar for both products.

Reviewer's Comments:
The geometric mean concentration-time profile following single dose of 180 µg Albuterol MDPI or ProAir HFA inhalation is presented in Figure 4.5.

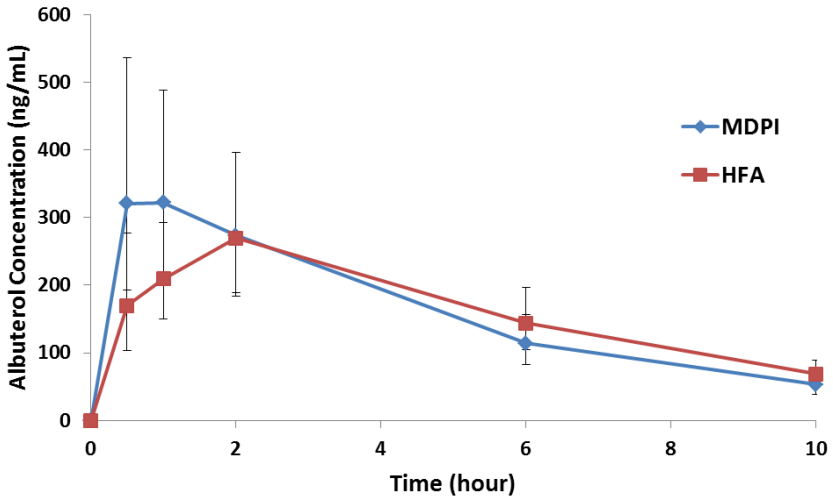


Figure 4.5 Geometric mean plasma concentration-time profiles (PK set) of albuterol following single-dose (180 µg) inhalation via Albuterol MDPI (blue, N=13) or ProAir HFA (red, N=13). (Source: Reviewer's analysis)

The PK parameters derived from full set (N=15) are summarized in Table 4.6. The geometric mean AUC_{0-t} of albuterol was comparable between two products with1695 (CV = 35%) pg·h/mL for Albuterol MDPI and 1823 (CV = 53%) for ProAir HFA after single-dose inhalation (Table 4.5). The geometric mean C_{max} was comparable between two products with 354 (CV = 41%) pg/mL for Albuterol MDPI and 309 (CV = 64%) for ProAir HFA. The median t_{max} of albuterol were 1.0 hour and 2.0 hour for Albuterol MDPI and ProAir HFA, respectively. The variation increased for PK parameters from ProAir HFA treatment group when full set was used for analysis. This is because the pre-dose albuterol concentration of Subject 10538012 was 19% of C_{max} value when treated with ProAir HFA.

Table 4.6 Geometric Mean (CV%) of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Children Aged 6-11 Years Old (Full Set)

PK parameters	Albuterol MDPI	ProAir HFA
Patient N	13	13
AUC_{0-t} (pg·h/mL)	1695 (35%)	1823 (53%)
C_{max} (pg/mL)	354 (41%)	309 (64%)
AUC_{0-inf} (pg·h/mL)	1980 (33%)	2317 (47%)
t_{max} (hour)*	1.0 (0.5, 2.0)	2.0 (0.5, 2.0)
$t_{1/2}$ (hour)	3.4 (23%)	4.1 (28%)

*** Median (range)**
Source: adapted from CSR 102, page 57, Table 7

The geometric mean concentration-time profile following single dose of 180 µg Albuterol MDPI or ProAir HFA inhalation is presented in Figure 4.6.

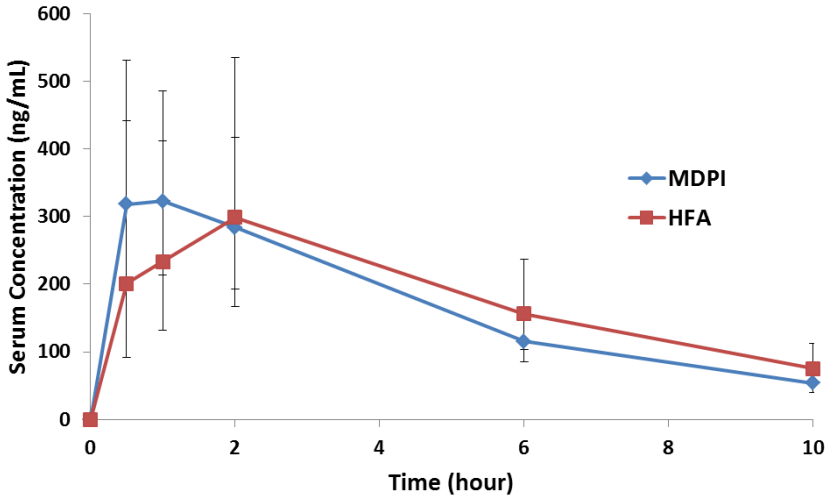


Figure 4.6 Geometric mean plasma concentration-time profiles (full set) of albuterol following single-dose (180 µg) inhalation via Albuterol MDPI (blue, N=13) or ProAir HFA (red, N=13). (Source: Reviewer's analysis)

4.1.2 Study ABS-AS-202

Study Type: Phase 2, PD/efficacy, safety, single-dose-ranging study in asthma children (4-11 yo)

Title: A Single-Dose, Multi-Center, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Five-Period Crossover, Dose-Ranging Efficacy and Safety Comparison of Albuterol Spiromax® and ProAir® HFA in Pediatric Patients with Persistent Asthma

Objective:
Primary Objective: To evaluate the efficacy of Albuterol MDPI and ProAir HFA at 2 dose levels relative to placebo.

Secondary Objectives: To evaluate safety of Albuterol Spiromax and ProAir HFA

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 5-treatment, 5-period, 10-sequence, 5-way crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in children (4 to 11 years of age) with persistent asthma. Each treatment period visit was separated by a 2-7-day washout period. Total 56 patients were planned to be enrolled; data from 61 patients were analyzed for efficacy and safety. No PK samples were collected.

Noteworthy inclusion criteria:

- Male or pre-menarchal female 4-11 years of age, inclusive, as of the screening visit.
- Documented physician diagnosis of persistent asthma of a minimum of 6 months duration that was stable for at least 4 weeks prior to the screening visit.
- FEV1 60-90% predicted for age, height, and sex at the screening visit based on the pediatric population standards.
- Reversible bronchoconstriction as verified by a ≥15% increase in baseline FEV1 within 30 minutes following inhalation of 180 mcg of albuterol.
- Maintained on stable dose (4 weeks minimum) of low-dose inhaled corticosteroids (≤200 µg of fluticasone propionate per day or equivalent), leukotriene modifiers, inhaled cromones, or on β2-agonists alone as needed.

Noteworthy exclusion criteria:

- Any asthma exacerbation requiring systemic corticosteroids within 3 months of the screening visit or any hospitalization for asthma within 6 months prior to the screening visit.
- Use of any prohibited concomitant medications within the washout period prescribed per protocol prior to the screening visit (oral, IM, IV, and intra-articular corticosteroids are prohibited to use within 6 weeks prior to the screening visit).

The four single-dose active treatments were:

- 90 µg albuterol via Albuterol MDPI
- 180 µg albuterol via Albuterol MDPI
- 90 µg albuterol via ProAir HFA
- 180 µg albuterol via ProAir HFA

Treatments were administered in a double-blind manner to eliminate any potential observer and/or patient bias. Blinding of the treatments in this study was accomplished using a double-blind, double-dummy procedure such that both the treatment and the dose level were blinded. Blinding was achieved by

providing 4 inhalers (2 identical MDIs and 2 identical MDPIs) to each patient for concurrent use in combinations.

Primary Endpoints:
Efficacy:

- The primary efficacy endpoint for this study was the baseline-adjusted percent-predicted FEV1 (PPFEV1) AUC_{0-6} after dosing.
- The secondary efficacy variable was the baseline-adjusted FEV1 AUC_{0-6}.
- Other endpoints:
  1. Baseline-adjusted maximum FEV1 ($FEV1_{max}$) within 6 hours after treatment
  2. Baseline-adjusted maximum PPFEV1 ($PPFEV1_{max}$) within 6 hours after treatment
  3. Time in minutes to 15% response onset (change in PPFEV1 of ≥15% from baseline) in patients who exhibited an increase in baseline PPFEV1 of at least 15% within 30 minutes after treatment
  4. Time in minutes to 12% response onset (change in PPFEV1 of ≥12% from baseline) in patients who exhibited an increase in baseline PPFEV1 of at least 12% within 30 minutes after treatment
  5. Time in minutes to maximum PPFEV1
  6. Duration in hours of 15% response
  7. Duration in hours of 12% response
  8. Response rate as based on a ≥15% increase in baseline PPFEV1 within 30 minutes after treatment
  9. Response rate as based on a ≥12% increase in baseline PPFEV1 within 30 minutes after treatment

The baseline for FEV1 evaluations on each treatment day was taken as the average of the 2 FEV1 determinations (measured at 30 minutes and again within 5 minutes prior to the commencement of study drug administration). Post-dose FEV1 evaluations were measured at 5 (±2), 15 (±5), 30 (±5), 45 (±5), 60 (±5), 120 (±5), 180 (±5), 240 (±5), 300 (±5), and 360 (±5) minutes after completion of study drug administration.

The primary statistical tool was the mixed-effect analysis of variance (ANOVA) with fixed effects of baseline FEV1 as a covariate, sequence, treatment group, period, and center, and random effect for subject within sequence.! The primary efficacy endpoint (FEV1 $AUEC_{0-6}$ in L*hr) with the comparison of interest being tested at the 2-sided 0.05 significance level in a sequential manner as follows: Albuterol Spiromax 180 mcg versus placebo; Albuterol Spiromax 90 mcg versus placebo, ProAir HFA 180 mcg versus placebo, and ProAir HFA 90 mcg versus placebo. If a test was not significant at this level, no further tests were done.

Vital signs: blood pressure, pulse rate were measured within 5 minutes prior to the scheduled time of FEV1 measurements over 4 hours after dosing.

Demography:
The demographic characteristics for the 61 randomized subjects who received treatment (Full Analysis Set) are summarized in Table 4.7.

Table 4.7 Demographic Characteristics (Full Analysis Set)

Demographic Variables		Total (N=61)
Age (years)	Mean (SD)	9.0 (1.59)
	Median (range)	9.0 (4, 11)
Sex	Male (%)	38 (62%)
	Female (%)	23 (38%)
Race	White (%)	28 (46%)
	Black (%)	29 (48%)
	Asian (%)	1 (2%)
	Other (%)	3 (5%)
Body Weight (kg)	Mean (SD)	38.2 (12.76)
	Median (range)	36.0 (19.1, 93.9)
Height (cm)	Mean (SD)	138.7 (10.21)
	Median (range)	137.0 (112.0, 160.0)
BMI (kg/m^2)	Mean (SD)	19.5 (4.35)
	Median (range)	18.5 (14.0, 38.1)

(Source: adapted from CSR ABS-AS-202, Page 106-107, Summary 15.1.2)

Efficacy Results:

Primary endpoint

Mean Baseline FEV1 values were similar for each of the 5 treatment arms, ranging from 1.47 to 1.52 L (Table 4.8). The baseline PPFEV1 values were also similar cross 5 treatments, ranging from 73.8% to 75.7%.

Table 4.8 Mean (SD) of Baseline FEV1 (L) by Treatment (Full Analysis Set)

!

Treatment	Subject N	FEV1 (L)*	PPFEV1 (%)
Albuterol MDPI (90 ug)	58	1.48 (0.29)	74.3 (6.17)
Albuterol MDPI (180 ug)	58	1.48 (0.28)	75.1 (6.57)
ProAir HFA (90 ug)	59	1.47 (0.28)	73.8 (6.78)
ProAir HFA (180 ug)	60	1.52 (0.30)	75.7 (6.58)
Placebo	59	1.49 (0.28)	75.4 (6.45)

*** Arithmetic mean (SD)**

Source: adapted from CSR 202, page 117 and 119, Summary 15.2.1.1

Following each single-dose, active treatment of albuterol inhalation, there was an overall increase in mean PPFEV1 at each 6-hour post-dose time point with peak mean PPFEV1 achieved approximately at 45 minutes post-dose (Figure 4.7). The PPFEV1 then decreased gradually, but still were above the baseline at 6 hour post-dose. All active treatments were significantly superior to placebo (Table 4.9). There was no difference between Albuterol MDPI 90 µg and 180 µg (p=0.7772), whereas ProAir HFA 180 µg was superior to 90 µg (p=0.0226).

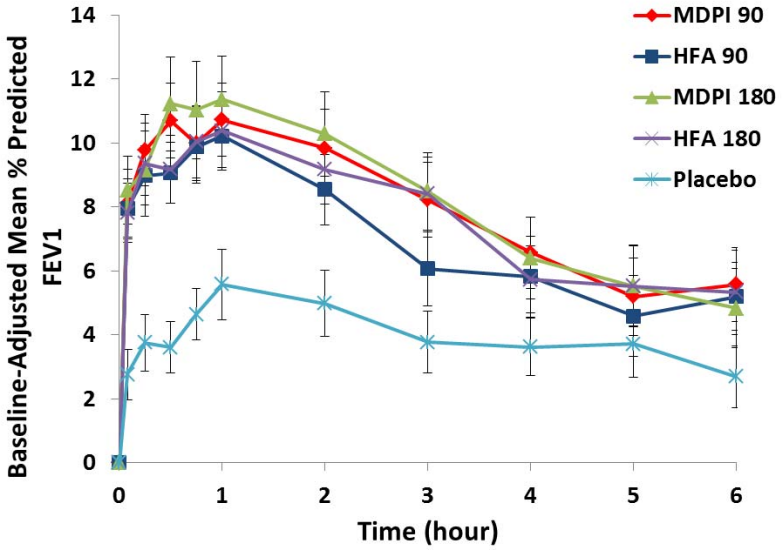


Figure 4.7 Arithmetic baseline-adjusted mean PPFEV1 following single-dose albuterol delivered as Albuterol MDPI 90 µg (red), Albuterol MDPI 180 µg (green), ProAir HFA 90 µg (blue), ProAir HFA 180 µg (purple), and placebo (cyan), respectively. Error bars represent the standard error. (Source: adapted from CSR202 page 66, Figure 2)

Table 4.9 Statistical Analysis of Baseline-Adjusted PPFEV1 AUC_{0-6} (%•hour) (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n	59	58	59	59	59
Mean±SE	25.4±6.25	46.6±6.27	48.0±6.24	37.9±6.25	49.1±6.26
95% CI	12.94, 37.81	34.13, 59.07	35.56, 60.39	25.43, 50.30	36.61, 61.50
Active-Placebo					
Mean±SE		21.2±4.87	22.6±4.87	12.5±4.85	23.7±4.85
95% CI		11.6, 30.81	13.00, 32.20	2.93, 22.05	14.13, 33.23
P-value		**<0.0001**	**<0.0001**	**0.0107**	**<0.0001**
90 mcg-180 mcg					
Mean±SE			-1.4±4.88		-11.2±4.87
95% CI			-11.00, 8.23		-20.80, -1.59
P-value			0.7772		**0.0226**

Source: CSR 202, page 64, Table 9

Secondary endpoint

Following each single-dose, active treatment of albuterol inhalation, there was an overall increase in mean FEV1 at each 6-hour post-dose time point with peak mean FEV1 achieved approximately at 45 minutes post-dose (Figure 4.8). The FEV1 then decreased gradually, but still were above the baseline at 6 hour post-dose. All active treatments were significantly superior to placebo (Table 4.10). There was no difference between Albuterol MDPI 90 µg and 180 µg (p=0.6342), whereas ProAir HFA 180 µg was superior to 90 µg (p=0.0488).

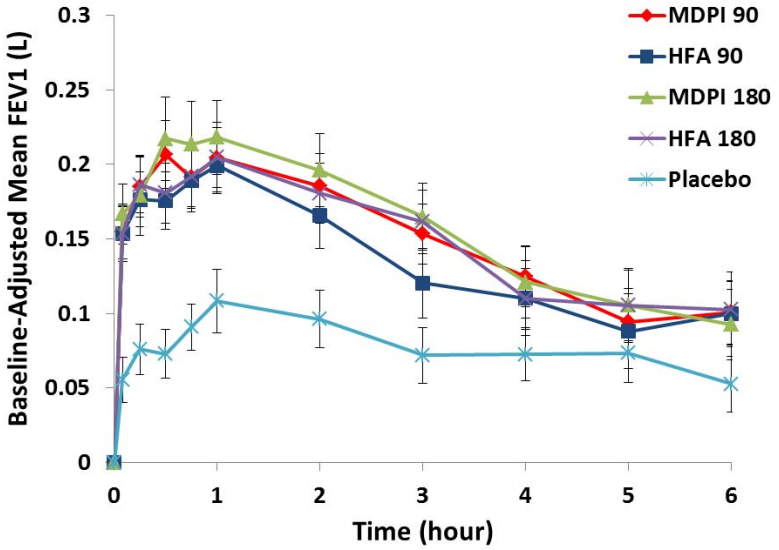


Figure 4.8 Arithmetic baseline-adjusted mean FEV1 following single-dose albuterol delivered as Albuterol MDPI 90 µg (red), Albuterol MDPI 180 µg (green), ProAir HFA 90 µg (blue), ProAir HFA 180 µg (purple), and placebo (cyan), respectively. Error bars represent the standard error. (Source: adapted from CSR202 page 69, Figure 4)

Table 4.10 Statistical Analysis of Baseline-Adjusted FEV1 AUC_{0-6} (L•hour) (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n	59	58	59	59	59
Mean±SE	0.48±0.14	0.88±0.14	0.93±0.14	0.74±0.14	0.93±0.14
95% CI	0.20, 0.76	0.60, 1.16	0.65, 1.20	0.46, 1.02	0.65, 1.21
Active-Placebo					
Mean±SE		0.40±0.10	0.45±0.10	0.26±0.10	0.45±0.10
95% CI		0.21, 0.59	0.26, 0.64	0.08, 0.45	0.26, 0.64
P-value		**<0.0001**	**<0.0001**	**0.0062**	**<0.0001**
90 mcg-180 mcg					
Mean±SE			-0.05±0.10		-0.19±0.10
95% CI			-0.23, 0.14		-0.38, 0.00
P-value			0.6342		**0.0488**

Source: CSR 202, page 67, Table 10

Other endpoint

- **Baseline-Adjusted Maximum FEV1 over 6 Hours**

Following each single-dose, active treatment of albuterol inhalation, the maximum increase of FEV1 from baseline within 6-hour post-dose period was significantly superior to placebo (Table 4.11). There was no significant difference between 90 µg and 180 µg for both products.

Table 4.11 Comparisons of Baseline-Adjusted Maximum FEV1 (L) over 6 Hours Post-Dose (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n	59	58	59	59	59
Mean±SE	0.19±0.02	0.27±0.02	0.28±0.02	0.26±0.02	0.29±0.02
95% CI	0.14, 0.24	0.23, 0.32	0.24, 0.33	0.21, 0.31	0.24, 0.34
Active-Placebo					
Mean±SE		0.09±0.02	0.10±0.02	0.07±0.02	0.10±0.02
95% CI		0.05, 0.12	0.06, 0.13	0.04, 0.10	0.07, 0.14
P-value		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
90 mcg-180 mcg					
Mean±SE			-0.01±0.02		-0.03±0.02
95% CI			-0.04, 0.02		-0.06, 0.00
P-value			0.5421		0.0688

Source: CSR 202, page 70, Table 11

- **Baseline-Adjusted Maximum PPFEV1 over 6 Hours**

Following each single-dose, active treatment of albuterol inhalation, the maximum increase of PPFEV1 from baseline within 6-hour post-dose period was significantly superior to placebo (Table 4.12). There was no difference between Albuterol MDPI 90 µg and 180 µg (p=0.5578), whereas ProAir HFA 180 µg was superior to 90 µg (p=0.0407).

Table 4.12 Comparisons of Baseline-Adjusted Maximum PPFEV1 (%) over 6 Hours Post-Dose (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n	59	58	59	59	59
Mean±SE	9.83±1.15	14.21±1.16	14.71±1.15	13.21±1.15	14.97±1.15
95% CI	7.53, 12.12	11.91, 16.51	12.42, 17.00	10.91, 15.50	12.67, 17.26
Active-Placebo					
Mean±SE		4.38±0.85	4.88±0.85	3.38±0.85	5.14±0.85
95% CI		2.70, 6.06	3.20, 6.57	1.70, 5.06	3.47, 6.81
P-value		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
90 mcg-180 mcg					
Mean±SE			-0.50±0.86		-1.76±0.85
95% CI			-2.19, 1.18		-3.44, -0.08
P-value			0.5578		**0.0407**

Source: CSR 202, page 71, Table 12

- **Time to Onset 15% Response**

The time to 15% response onset, defined as the first time that an increase from baseline in PPFEV1 of at least 15% was noted within 30 minutes after treatment, was determined for the 4 active treatment groups (Table 4.13). The median time to 15% response onset for Albuterol MDPI was about 8.0 to 8.8 minutes, comparable to 8.4 minutes for ProAir HFA.

Table 4.13 Time (minutes) to 15% Response among Responders within 30 Minutes (Full Analysis Set)

Statistic	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
n	26	27	22	24
Mean±SD	10.7±4.79	10.4±6.96	9.4±5.41	12.8±7.88
Median	8.8	8.0	8.4	8.4
Min, max	4.8, 18.5	4.7, 29.7	4.0, 26.6	4.2, 28.7

Source: CSR 202, page 72, Table 13

- **Time to Maximum PPFEV1 Response**

The time to maximum PPFEV1response was summarized for the 5 treatment groups (Table 4.14). The mean time to time to maximum PPFEV1response for Albuterol MDPI (both doses) was about 45 to 47.6 minutes, comparable to 44.7 minutes to 50.1 minutes for ProAir HFA.

Table 4.14 Time (minutes) to Maximal PPFEV1 over 6 Hours (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n	59	58	59	59	59
Mean	75.9	47.6	45.0	50.1	44.7
95% CI	57.9, 99.5	36.2, 62.5	34.3, 59.0	38.2, 65.7	34.1, 58.6
Active/Placebo		0.63	0.59	0.66	0.59
95% CI		0.43, 0.91	0.41, 0.86	0.46, 0.95	0.41, 0.85
P-value		**0.0130**	**0.0054**	**0.0265**	**0.0048**
90 mcg/180 mcg			1.06		1.12
95% CI			0.73, 1.53		0.78, 1.62
P-value			0.7667		0.5363

Source: CSR 202, page 73, Table 15

- **Duration of a 15% Response**

The duration of 15% response, as measured in patients meeting the 15% response criterion within 30 minutes after treatment dosing, was summarized for the 4 active treatment groups (Table 4.15). The duration of 15% response was 2.8-3.0 hours for Albuterol MDPI (both doses) and ProAir HFA 180 µg, but was numerically shorter for ProAir HFA 90 µg (2.4 hours).

Table 4.15 Duration of 15% Response among Responders within 30 Minutes (Full Analysis Set)

Statistic	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
n	26	27	22	24
Mean±SD	2.8±2.37	3.0±2.29	2.4±2.21	2.8±2.48
Median	2.8	2.9	1.9	2.3
Min, max	0.2, 5.9	0.1, 5.9	0.2, 5.9	0.2, 5.9

Source: CSR 202, page 74, Table 16

- **Response Rate Based on 15% Increase in PPFEV1**

The response rate as based on a ≥15% increase in baseline PPFEV1 within 30 minutes after dosing was determined for the 5 treatment groups. The response rate was only 17% for the placebo patients, 45-46% for Albuterol MDPI, and 37-41% for ProAir HFA (Table 4.16). The response rates for all active treatments were significantly superior to placebo. There was no significant difference on response rate between 90 µg and 180 µg for both products.

Table 4.16 Response Rate Based on 15% Increase in Baseline PPFEV1 within 30 Minutes (Full Analysis Set)

Statistic	Placebo (N=61)	Albuterol MDPI 90 mcg (N=61)	Albuterol MDPI 180 mcg (N=61)	ProAir HFA 90 mcg (N=61)	ProAir HFA 180 mcg (N=61)
n (%) responders	10 (17.0)	26 (44.8)	27 (45.8)	22 (37.3)	24 (40.7)
Model est rate±SE	0.10±0.04	0.43±0.09	0.43±0.09	0.30±0.08	0.37±0.09
95% CI	0.01, 0.18	0.24, 0.61	0.25, 0.62	0.14, 0.47	0.19, 0.54
Difference from Placebo±SE		0.33±0.09	0.34±0.09	0.21±0.08	0.27±0.09
95% CI		0.15, 0.51	0.15, 0.52	0.05, 0.37	0.10, 0.45
P-value		**0.0006**	**0.0005**	**0.0119**	**0.0027**
Difference Between Doses±SE			-0.01±0.11		-0.06±0.10
95% CI			-0.22, 0.21		-0.26, 0.14
P-value			0.9490		0.5279

Source: CSR 202, page 75, Table 18

PD/Vital Signs Results:

- **The maximum increase from baseline in systolic blood pressure**

The systolic blood pressure increased following all 4 active treatments.! The mean maximum increases from baseline ranged from 3.4 to 4.8 mmHg in 4 active treatment groups (Table 4.17). There was no significant difference between two products (Albuterol MDPI-ProAir HFA) at both 90 µg level [1.12 (90% CI=-0.37, 2.60)] and 180 µg level [-0.91 (90% CI=-2.40, 0.58)].

Table 4.17 Maximum Increase from Baseline in Systolic Blood Pressure Over 4 Hours Post-Dose by Treatment

Treatment	Subject N	Maximal Increase from Baseline in Systolic Blood Pressure (mmHg)*
Albuterol MDPI (90 µg)	58	4.79 (2.58, 6.99)
Albuterol MDPI (180 µg)	58	3.36 (1.20, 5.52)
ProAir HFA (90 µg)	59	3.67 (1.50, 5.85)
ProAir HFA (180 µg)	59	4.28 (2.11, 6.44)

*** mean (95% CI)**
Source: adapted from CSR 202, page 189, Summary 15.3.11

- **The maximum decrease from baseline in diastolic blood pressure**

The diastolic blood pressure decreased following all 4 active treatments.¦The mean maximum decreases from baseline ranged from 1.9 to 2.7 mmHg in 4 active treatment groups (Table 4.18). There was no significant difference between two products (Albuterol MDPI-ProAir HFA) at both 90 µg level [-0.18 (90% CI=-1.40, 1.04)] and 180 µg level [-0.53 (90% CI=-1.75, 0.70)].

Table 4.18 Maximum Decrease from Baseline in Systolic Blood Pressure Over 4 Hours Post-Dose by Treatment

Treatment	Subject N	Maximal Decrease from Baseline in Diastolic Blood Pressure (mmHg)*
Albuterol MDPI (90 µg)	58	2.49 (0.61, 4.36)
Albuterol MDPI (180 µg)	58	1.87 (0.02, 3.72)
ProAir HFA (90 µg)	59	2.67 (0.81, 4.52)
ProAir HFA (180 µg)	59	2.40 (0.55, 4.24)

*** mean (95% CI)**
Source: adapted from CSR 202, page 190, Summary 15.3.12

- **The maximum increase from baseline in pulse rate**

The pulse rate increased following all 4 active treatments.¦The mean maximum increases from baseline ranged from 5.4 to 6.2 mmHg in 4 active treatment groups (Table 4.19). There was no significant difference between two products (Albuterol MDPI-ProAir HFA) at both 90 µg level [-0.67 (90% CI=-2.31, 0.96)] and 180 µg level [0.10 (90% CI=-1.54, 1.75)].

Table 4.19 Maximum Increase from Baseline in Pulse Rate Over 4 Hours Post-Dose by Treatment

Treatment	Subject N	Maximal Increase from Baseline in Pulse Rate (bpm)*
Albuterol MDPI (90 µg)	58	5.53 (3.01, 8.05)
Albuterol MDPI (180 µg)	58	5.53 (3.05, 8.00)
ProAir HFA (90 µg)	59	6.21 (3.72, 8.70)
ProAir HFA (180 µg)	59	5.42 (2.94, 7.90)

*** mean (95% CI)**
Source: adapted from CSR 202, page 191, Summary 15.3.13

- **ECG Findings**

ECG was conducted at the screening visit only. Only one randomized patient (#10577012) had a clinically significant abnormal ECG at screening consisting of left atrial rhythm and possible biventricular hypertrophy. However, the result of a retest ECG conducted 2 days later was normal and the patient was permitted to enter the study.

Conclusions:

- Efficacy:

Single dose albuterol at 90 µg or 180 µg delivered by MDI or the new MDPI device was significantly superior to placebo in improving the primary variable, baseline-adjusted PPFEV1 AUC_{0-6} and the secondary variable, baseline-adjusted FEV1 AUC_{0-6}. The improvements were comparable between two products. There was no significant difference on improvements between 90 µg or 180 µg delivered by MDPI.

Albuterol MDPI at 90 µg or 180 µg resulted in a median onset of 15% response within 10-11 minutes, a peak effect at 45-48 minutes and duration of response of 2.8-3.0 hours in pediatric patients. The response rate is approximately 45%. The responses to Albuterol MDPI were similar to the responses to ProAir HFA.

- Safety:

Values of changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure and heart rate) appeared similar between Albuterol MDPI and ProAir HFA at both dose levels. Generally the changes from baseline were numerically small and might not have clinical relevant meanings.

4.2 Appendix – Supplemental New Drug Application Filing and Review Form

Application Information			
sNDA Number	205636	**SDN**	73
Applicant	Teva	**Submission Date**	**6/29/2015**
Generic Name	Albuterol sulfate	**Brand Name**	ProAir Respiclick
Drug Class	Short-acting beta-adrenergic agonist		
Indication	• Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. • Prevention of exercise-induced bronchospasm in patients 4 years of age and older		
Dosage Regimen	• Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient. • Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise.		
Dosage Form	Multi-dose breath-actuated dry powder inhaler delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation.	**Route of Administration**	Inhalation
OCP Division	II	**OND Division**	DPARP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Yunzhao Ren MD, Ph. D	Suresh Doddapaneni, Ph.D.	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	8/12/2015	**74-Day Letter Date**	9/12/2015
Review Due Date	12/3/2015	**PDUFA Goal Date**	4/29/2016

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑ Yes ✗ No If no list reason(s)
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ✗ Yes ☑ No If yes list comment(s)
Is there a need for clinical trial(s) inspection? ✗ Yes ☑ No If yes explain

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

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☑ Bioanalytical methods		1	Study ABS-AS-102
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Study ABS-AS-102
	☐Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	Study ABS-AS-102
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		1	Study ABS-AS-102
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			

☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies/Reports		**In Vitro**		**In Vivo**	1
Total Number of Studies/Reports to be Reviewed					1

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03/24/2016