

## CLINICAL REVIEW

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Division / Office	DPARP/ODE II
Reviewer Name	Keith M Hull, MD, PhD
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Established Name	Albuterol Sulfate
(Proposed) Trade Name	ProAir RespiClick
Therapeutic Class	$\beta_2$ -adrenergic receptor agonist
Applicant	Teva
Formulation	Multi-dose Dry Powder Inhaler <u>Metered dose:</u> 108 mcg albuterol sulfate <u>Delivered dose:</u> 90 mcg albuterol base
Dosing Regimen	1. Two inhalations Q4-6 h 2. Two inhalations 15-30 prior to exercise
Indication	1. treatment/prevention of bronchospasm 2. prevention of exercise-induced bronchospasm
Intended Population(s)	Patients with persistent asthma or exercise-induced asthma age 4 years and older

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## **1 Recommendations/Risk Benefit Assessment**

Teva Pharmaceuticals (Sponsor) is submitting a supplemental 505(b)(2) New Drug Application (sNDA) for Albuterol Multidose Dry Powder Inhaler (Albuterol MDPI) with the proposed tradename *ProAir RespiClick* to treat bronchospasm in patients 4 years of age and older. Albuterol MDPI contains albuterol sulfate and lactose and has been formulated to provide comparable delivery of albuterol to ProAir HFA Inhalation Aerosol (NDA 021457).

### **1.1 Recommendation on Regulatory Action**

This reviewer recommends approval of Albuterol HFA (ProAir RespiClick) for the following indications:

- 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

### **1.2 Risk Benefit Assessment**

The Sponsor aimed to develop Albuterol MDPI to be comparable to ProAir HFA such that both products delivered equivalent 90 mcg doses of albuterol base per device actuation with the intent that Albuterol MDPI could be dosed in the same manner as ProAir HFA. The Sponsor's original NDA for ProAir RespiClick was approved on March 31, 2015 for patients 12 years of age and older. The current submission contains clinical data to support the inclusion of treating children ages 4 to 11 years old, thus broadening the indication for use to treat bronchospasm in patients 4 years of age and older.

Although not strictly designed to analyze for non-inferiority or comparability, the data from Studies ABS-AS-102 and -202 demonstrated similar single-dose efficacy and

safety profiles of Albuterol MDPI and ProAir HFA in children 4 to 11 years of age who were diagnosed with persistent asthma. Both studies met their primary endpoints assessing FEV<sub>1</sub> and analysis of the pharmacodynamic and pharmacokinetic parameters further supported a high degree of clinical similarity between Albuterol MDPI and ProAir HFA at each of the five doses. Additional analysis of the data did not demonstrate a difference in the onset of action of albuterol between either of the two products. Overall, these studies support the Sponsor's proposed dosing of Albuterol MDPI up to 180 mcg.

Study ABS-AS-303 comprised the primary focus for the safety evaluation, as well as efficacy, given the overall study design, large subject cohort, and placebo-controlled period. The study was designed to support the efficacy and safety of Albuterol MDPI at the proposed recommended dosing in children ages 4 to 11 years old that were diagnosed with persistent asthma. The study met its primary endpoint demonstrating that subjects treated with Albuterol-MDPI 180 mcg experienced clinically meaningful and statistically significant increases in the baseline-adjusted percent-predicted FEV<sub>1</sub> versus time curve over six hours after dosing (PPFEV<sub>1</sub> AUC<sub>0-6</sub>) compared to placebo-treated subjects over the 3-week controlled period. Analyses of the secondary endpoints were supportive of the primary endpoint and together the data confirm the known effectiveness of albuterol in subjects with asthma.

The Sponsor did not conduct specific studies to support the use of Albuterol MDPI for the treatment of exercise-induced bronchospasm in children 4 to 11 years of age but rather relied on extrapolation of the known efficacy and safety of Albuterol MDPI, and albuterol in general, in children with asthma and the known pathophysiology of exercise-induced bronchospasm and the mechanism of action of albuterol. The extrapolation of data to include the indication of exercise-induced bronchospasm was agreed to with the Sponsor during regulatory meetings in support of the current submission. This reviewer agrees that the claim to treat exercise-induced bronchospasm should be extended to include children ages 4 to 11 years old.

Overall, these studies demonstrated a clinically meaningful benefit and acceptable safety profile of Albuterol MDPI in patients with persistent asthma at the recommended dosing.

Safety data from Studies ABS-AS-102, -202, and -303 provide the pivotal safety information for Albuterol MDPI in children ages 4 to 11 years old. These three studies, in conjunction with the well known safety profile of inhaled albuterol and the recently approved Albuterol MDPI device in patients ages 12 years and older, allows for adequate analyses to identify potential safety signals.

No deaths, serious adverse events, or discontinuations occurred during Studies ABS-AS-102, -202, and -303, although two subjects reported a serious adverse event during the placebo run-in period of Study ABS-AS-303. In general, the percentage of subjects reporting adverse events was either similar between treatment arms or slightly greater in placebo-treated subjects. Headache was the most commonly reported adverse event reported in  $\geq 2\%$  of subjects and greater in the Albuterol MDPI treatment arm.

Overall, analysis of the safety data did not demonstrate an important safety signal with the use of Albuterol MDPI and the results support the safety of Albuterol MDPI in the treatment or prevention of bronchospasm in patients 4 years of age and older with bronchospasm.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No postmarketing risk evaluation and mitigation strategies are being recommended at this time.



#### **1.4 Recommendations for Postmarket Requirements and Commitments**

No clinically oriented postmarketing requirements or commitments are being recommended at this time.

## 2 Introduction and Regulatory Background

Asthma affects the airway passages of the lungs and is characterized by airway inflammation and bronchial hyper-responsiveness. During acute asthmatic episodes, the airway passages become narrower and more obstructed, resulting in coughing, wheezing, tightness of the chest, shortness of breath, and increased mucus production. It is believed that these asthma symptoms may be associated with chronic changes in airway structure and function, increasing the morbidity and mortality of those affected.

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. Asthma contributed to over 1.3 million visits to hospital outpatient departments with asthma listed as the primary diagnosis and to 1.8 million emergency department visits in 2010, leading to over 439,000 patients requiring hospitalization with an average length of hospital stay of four days.

Short-acting  $\beta$ 2-adrenergic agonists, such as albuterol, are a mainstay of asthma management and are the recommended drugs for relief of acute asthmatic symptoms and prophylaxis for exercise-induced bronchoconstriction. They are not intended to modify the disease process and are taken as needed for relief of symptoms. The use of  $\beta$ 2-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. For this reason, early consideration should be given to adding anti-inflammatory agents, such as corticosteroids, to the therapeutic regimen.

Inhaled albuterol aerosols are the most commonly prescribed treatments for the relief of bronchospasm and is the preferred route of delivery to treat asthma as it delivers relatively low but effective doses of medication to the site of action; results in rapid delivery of locally high drug concentrations of drug; largely bypasses issues arising from drug metabolism; avoids many of the complications of systemic side effects; and provides the patient with rapid and convenient access to treatment.

Albuterol has been available clinically for over 30 years and its efficacy and safety profiles are well documented. The clinical use of albuterol is in accordance with current treatment guidelines for the management of asthma and other obstructive lung diseases that require the use of short acting  $\beta$ 2- agonists.

The pharmacologic effects of albuterol are attributable to activation of  $\beta$ 2-adrenergic receptors on airway smooth muscle, which results in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles, and acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against most bronchoconstrictor challenges.

## 2.1 Product Information

Albuterol Multidose Dry Powder Inhaler (Albuterol MDPI) contains a formulation of albuterol sulfate ((b) (4) mg per device) and lactose monohydrate ((b) (4) g per device). The device is marketed as a novel breath-actuated, dry powder inhaler with integrated dose counter that is designed to deliver a metered dose of 90 mcg of albuterol base from the inhaler mouthpiece; however, to achieve this final concentration of albuterol at the mouthpiece, each actuation actually loads 97 mcg of albuterol base, or 117 mcg of albuterol sulfate (labeled strength). (b) (4)

[REDACTED]

[REDACTED]

The Sponsor is currently approved for use of the Albuterol MDPI (ProAir RespiClick) 180 mcg for the treatment and prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and/or exercise-induced bronchospasm. The current submission is a supplemental NDA for the same indication but proposed extension of the targeted population to patients 4 years of age and older.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1. Currently Available Treatments for the Treatment of Bronchospasm**

<b>Inhaled corticosteroids</b>		
Generic Name	Brand Name	Dosage
Beclomethasone Propionate HFA	QVAR Inhalation Aerosol	40/80 mcg/inhalation
Budesonide	Pulmicort Flexhaler	90/180 mcg/inhalation
	Pulmicort Respules	0.25/0.5/1 mg/2 mL suspension
Ciclesonide	Alvesco Inhalation Aerosol	80/160 mcg/inhalation
Flunisolide	Aerobid Aerosol	250 mcg/inhalation
	Aerobid-M Aerosol	250 mcg/inhalation
	Aerospan	80 mcg/inhalation
Fluticasone Furoate	Arnuity Ellipta	100/200 mcg/inhalation
Fluticasone Propionate	Flovent HFA	44/110/220 mcg/inhalation
	Flovent Diskus	50/100/250 mcg/inhalation
Mometasone	Asmanex Twisthaler	110/220 mcg/inhalation
Triamcinolone Acetonide	Azmacort Aerosol	75 mcg/inhalation
<b>Combination Inhalers</b>		
Generic Name	Brand Name	Dosage
Budesonide+Formoterol	Symbicort	80/160 mcg + 4.5 mcg/inhalation
Fluticasone+Salmeterol	Advair Diskus	100/250/550 mcg + 50 mcg/inhalation
	Advair HFA	45/115/230 mcg + 21 mcg/inhalation
Mometasone+Formoterol	Dulera	100/200 mcg + 5 mcg/inhalation
Umeclidinium+Vilanterol	Anoro Ellipta	62.5+25 mcg/inhalation
<b>Long-acting <math>\beta</math>-agonists</b>		
Generic Name	Brand Name	Dosage
Albuterol Sulfate	VoSpire ER tablets	4/8 mg tablets
Formoterol Fumarate	Foradil Aerolizer	12 mcg tablets
Salmeterol Xinafoate	Serevent Diskus	50 mcg/inhalation
Arformoterol Tartrate	Brovana	15 mcg/inhalation
Formoterol Fumarate	Perforomist	20 mcg/inhalation
<b>Leukotriene modifiers</b>		
Generic Name	Brand Name	Dosage
Montelukast	Singulair	4/5 mg tablets
Zafirlukast	Accolate	10/20 mg tablets
Zileuton	Zyflo CR	600 mg tablets
<b>Immunomodulators</b>		
Generic Name	Brand Name	Dosage
Omalizumab	Xolair	150 mg/vial
<b>Short-acting <math>\beta</math>-agonists</b>		
Generic Name	Brand Name	Dosage
Albuterol Sulfate HFA	ProAir/Ventolin HFA	90 mcg/inhalation
Albuterol Sulfate	Generic for nebuliza ion	0.083% and 0.5% solution
Ipratropium Bromide HFA	Atrovent HFA	17 mcg/inhalation
Ipratropium Bromide+Albuterol	Combivent/RespiMat	20 mcg+100 mcg/inhalation
Levalbuterol HCl	Xopenex	45 mcg/inhalation

### **2.3 Availability of Proposed Active Ingredient in the United States**

Albuterol sulfate is readily available in the USA in inhalation formulations (e.g., ProAir RespiClick and ProAir HFA) or as a solution for nebulization.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

Albuterol sulfate is a sympathomimetic amine with selective  $\beta_2$ -agonist properties and pharmacologic effects similar to terbutaline. When administered by inhalation or by the oral route, the primary effect is on the bronchial smooth muscle in the lungs acting as a bronchodilator. The onset of action is short with a clinically significant effect within 15 minutes after administration and lasting as long as four hours. Albuterol sulfate has been used clinically for over 30 years and the drug is well characterized with a known safety profile. The primary side effects are cardiovascular in nature that manifest clinically as tachycardia, hypertension, and changes in ECG.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

Given that the Sponsor's developmental program for RespiClick simultaneously conducted studies for the indication of patients  $\geq 12$  years of age as well as studies with children ages 4 to 11 years old, the presubmission regulatory activity related to the current submission will include regulatory activities regarding the initial NDA 205636/0000 submission.

A pre-Investigational New Drug meeting was held between the Sponsor and the Division on March 27, 2009, at which time the Division issued comments providing general guidance on the development program. Specifically, the Division recommended that the Sponsor's development program for Albuterol MDPI for adults and adolescents  $\geq 12$  years include the following:

- A single dose tolerability study in healthy subjects to assess for acute bronchospasm. Alternatively, clinical data with the same formulation could be used in place of an actual study
- A single-dose, dose-ranging, crossover, comparative efficacy and safety study in patients with asthma. The study was to compare Albuterol MDPI to a comparator product and placebo at a minimal of two dose levels
- An escalating, comparative, cumulative dose pharmacodynamic safety and efficacy study in patients with asthma with acute bronchospasm. The cumulative doses should include multiple escalating doses (i.e., 1, 1, 2, 4, and 8 puffs), administered 20-30 minutes apart
- Replicate 12-week, randomized, placebo-controlled, chronic dosing efficacy and safety studies in patients with asthma
- A long-term (12-month) safety study to assess the safety of the Albuterol MDPI formulation and device performance
- Pharmacokinetic assessment to generate data that will allow for characterization of albuterol exposure for the product and for comparative assessment to the comparator
- Assess the reliability and ruggedness of the Albuterol MDPI device and also the dose counter. The test strategy should include complete in vitro testing of all devices that are claimed by patients to have had a problem or failed, and a representative number of devices that have been used by patients in the clinical studies with no reported problem

The Division agreed with the Sponsor that an application under Section 505(b)(2) of the FD&C Act was appropriate for this product, except in the case where another pharmaceutically equivalent product was approved and an Abbreviated New Drug Application became appropriate. The Division also agreed in principle that further nonclinical studies were not needed, although characterization of impurities and

intermediates was requested. Additionally, the Division also noted that initiation of pediatric studies should await results from studies in adults.

An end-of-Phase 2 meeting was held on October 5, 2010 where the Division agreed that the design of the proposed phase 3 studies were generally acceptable but emphasized the need for diverse geographical locations across the USA with differing humidity, the need for assessment of the robustness and reliability of the MDPI device, the need for inclusion of protocols for dose counter and device performance assessment, and the need for collection of pharmacokinetic data from a subset of patients in a clinical study. The Division further commented that sufficient numbers of adolescents needed to be enrolled, that the sample size for Studies ABS-AS-301, -302, and -304 appeared to be adequate and that a single exercise-induced bronchospasm study was sufficient if the drug demonstrated efficacy in treatment or prevention of bronchospasm in patients  $\geq 12$  years of age. A pre-NDA meeting was held on December 16, 2013 where the Division reiterated that data should be submitted with the NDA to substantiate the reasoning for a waiver in children less than 4 years of age.

Three versions of the Albuterol MDPI device were used in clinical studies:

- NB6 was used in the first IVAX Spiromax studies outside the USA (Studies IX-100-076 and IX-101-076) which delivered 100 mcg albuterol sulfate
- NB7/2 was used in the supportive studies ABS-AS-101, ABS-AS-201, and ABS-AS-306
- NB8 was used in the pivotal safety studies in asthma: ABS-AS-301, -304 and -307.

The Sponsor discovered a problem with the NB7/2 device during Study ABS-AS-306 involving patients repeatedly opening and closing the mouthpiece cover of the device without inhaling following opening of the mouthpiece cover. This resulted in device failures during the study. Consequently, the Sponsor redesigned the device, NB8, which

was used in the pivotal phase 3 studies. Additionally, the NB8 device reliability was evaluated in Study ABS-AS-308.

At the time of submission for NDA 205636/0000, the Sponsor had received a Pediatric Deferral for children ages 4-11 years of age, and a Pediatric Waiver for children younger than four years of age.

The current submission contains of the pediatric clinical program studying Albuterol MDPI using the NB8 device in two studies that have been conducted in children age 4 to 11 years old. Study ABS-AS-102 was a comparison of the pharmacokinetic and pharmacodynamic profiles of the Albuterol MDPI to ProAir HFA in pediatric patients with persistent asthma. Study ABS-AS-202 was a single-dose, multicenter, randomized, double-blind, double-dummy, placebo-controlled, 5-period crossover, dose-ranging efficacy and safety comparison of the Albuterol MDPI to ProAir HFA, also in pediatric patients with persistent asthma.

Study ABS-AS-303 was conducted in children ages 4-11 years. This is a multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to compare the bronchodilator response to Albuterol MDPI relative to placebo in male and female subjects ages 4 to 11 years old with persistent asthma. The purpose of this study is to evaluate the chronic-dose efficacy and safety of Albuterol MDPI relative to placebo when administered to pediatric patients with persistent asthma for 3 weeks.



### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy.

Each of the pivotal studies reported protocol violations. A protocol violation was defined as departure from the approved protocol including nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or Good Clinical Practice guidelines, noncompliance to study drug administration, or use of prohibited medications. All protocol violations were reported to the responsible IRB/IEC, as required, and recorded by investigational center personnel on the case report form. Overall, the type and small numbers of protocol violations reported in the current application are not expected to compromise the quality of the data or to interfere with the ability to reach conclusions regarding the safety and efficacy of Albuterol MDPI in subjects with persistent asthma or exercise-induced asthma.

#### **3.2 Compliance with Good Clinical Practices**

All clinical studies were conducted in accordance with the clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56 and 312), and International Conference on Harmonization (ICH) Guidelines, that have their origin in the Declaration of Helsinki. All studies were registered with the clinical trials database ClinicalTrials.gov.

#### **3.3 Financial Disclosures**

The applicant has adequately disclosed financial arrangements with clinical

investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. Review of the submitted and signed Forms 3454: "Certification: Financial Interests and Arrangements of Clinical Investigators" does not raise concerns regarding the integrity of the submitted data to the current application.

The applicant also submitted completed and signed Forms 3455: "Disclosure: Financial Interest and Arrangement of Clinical Investigators" for five investigators:

- [REDACTED] (b) (6)
  - Studies ABS-AS- [REDACTED] (b) (6)
  - Speaker and consulting fees of \$39,310 (2013)

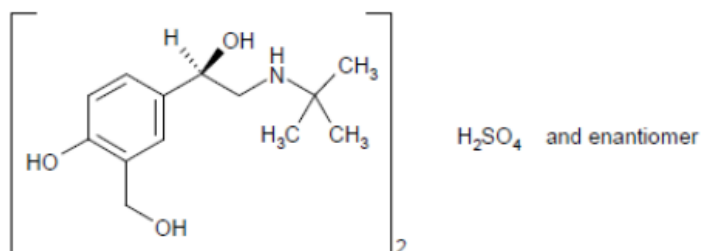
Overall, the number of subjects enrolled at the investigator's site was small compared to the total number of subjects enrolled in the overall study. In all cases, the applicant took steps to minimize potential bias which primarily consisted of excluding the investigator from the selection process of subjects, blinding to study drug, and exclusion from the knowledge and analysis of results. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The drug substance, albuterol sulfate, is the same drug substance used in ProAir HFA (Figure 1).

**Figure 1. Structural formula of Albuterol Sulfate**



Albuterol MDPI contains a formulation of albuterol sulfate (b) (4) mg per device) and lactose monohydrate (b) (4) g per device). The new device will be marketed as a novel breath-actuated, dry powder inhaler with integrated dose counter that is designed to deliver a metered dose of 90 mcg of albuterol base from the inhaler mouthpiece; however, to achieve this final concentration of albuterol at the mouthpiece, each actuation actually loads 97 mcg of albuterol base, or 117 mcg of albuterol sulfate (labeled strength). (b) (4)

(b) (4)

(b) (4)

The Chemistry, Manufacturing, and Controls (CMC) reviewer, Craig Bertha, PhD recommends approval of Albuterol MDPI based on his review of the data submitted to the application regarding the manufacturing of the drug substance and drug product. The reader is referred to the CMC review of Albuterol MDPI by Dr. Bertha for a detailed analysis of the CMC aspects related to this application.

### **4.3 Preclinical Pharmacology/Toxicology**

Albuterol sulfate has been used clinically to treat bronchoconstriction related to asthma for decades and has a well-characterized pharmacological mechanism and safety profile. The applicant's Albuterol MDPI provides a new delivery system for patients at the same dosage as that proven safe and effective in other products, e.g., ProAir HFA; however, no new safety signals were identified regarding the drug substance or container-closure system extractable/leachable profile.

The preclinical pharmacology and toxicology data were reviewed by Andrea Benedict, PhD who recommends approval of Albuterol MDPI based on her analysis of the data submitted to the application. The reader is referred to the nonclinical review by Dr. Benedict for a detailed analysis of the nonclinical pharmacology and toxicology aspects related to this application.

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action**

Albuterol is a short-acting  $\beta_2$ -adrenergic receptor agonist that acts as a bronchodilator and is used in the treatment of asthma and other forms of diffuse airway obstruction.

#### **4.4.2 Pharmacodynamics**

The pharmacokinetic and pharmacodynamic properties associated with the administration of Albuterol MDPI were thoroughly evaluated in the initial NDA for ProAir RespiClick and that the current sNDA references. Additionally, studies ABS-AS-102 and -202 were conducted in the current submission and further support the known pharmacodynamic effects of albuterol in children ages 4 to 11 years old. Clinically relevant aspects of the studies are discussed in Section 6 of this review; however, the reader is referred to the Clinical Pharmacology review by Yunzhao Ren, PhD for a

detailed analysis and discussion of the clinical pharmacology aspects related to this application.

#### 4.4.3 Pharmacokinetics

As noted above, the reader is referred to the Clinical Pharmacology review by Dr. Ren for a detailed analysis and discussion of the clinical pharmacology aspects related to the this application.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 2. Studies Used in the Efficacy and Safety Assessment of Albuterol MDPI**

Study	Study Location	Subjects Randomized (n)	Dosing	Study Design	Primary Objective
ABS-AS-102	USA	15	A-MDPI PA-HFA	Phase 1, open-label, crossover study in children ages 4-11 years old with persistent asthma	Comparison of A-MDPI 180 mcg vs. PA-HFA 180 mcg
ABS-AS-202	USA	61	A-MDPI PA-HFA	Phase 2, randomized, double-blind, placebo-controlled single-dose, 5-treatment, 5-way, crossover study in children ages 4-11 years old with persistent asthma	Assess efficacy and safety of 2 doses of A-MDPI vs. PA-HFA
ABS-AS-303	USA	185	A-MDPI PBO-MDPI	Phase 3, 3-wk, randomized, double-blind, placebo-controlled, repeat dose, parallel group study in children ages 4-11 years old with persistent asthma	Assess efficacy and safety of A-MDPI vs. PBO-MDPI
A-MDPI: Albuterol MDPI; PA-HFA: ProAir HFA; PK: pharmacokinetics					

### 5.2 Review Strategy

The clinical development program for Albuterol MDPI for children ages 4-11 years old, included three studies that were all conducted in the US (Table 2). All studies were completed as planned.

Except as noted above in Table 2, all of the submitted studies used to support the approval of Albuterol MDPI were designed as randomized, double-blind, placebo-controlled studies in which eligible subjects were randomized to double-blind study treatment following a run-in period.

FEV<sub>1</sub> measurements are routinely used clinically to assess the degree of airflow obstruction in patients presenting with asthma and are easily measured, reproducible, and accurately predicted based on age, sex, and height of individual patients. The assessment of FEV<sub>1</sub> as a primary endpoint is well accepted as a validated efficacy endpoint in studies assessing the safety and efficacy of drugs in subjects with asthma and each of the asthma studies submitted to the NDA assessed on-site measurement of FEV<sub>1</sub> for the primary efficacy endpoint using standardized methods based on generally accepted guidelines. Additionally, the Sponsor utilized a centralized spirometry data collection system incorporating a quality control program to reduce FEV<sub>1</sub> variability between and within patients and between each participating study site.

All subjects who were included in the current set of studies had a documented history of asthma and met the required predicted FEV<sub>1</sub> values and bronchoconstriction reversibility criteria required for each study inclusion criteria. The enrolled study subjects' baseline demographics and disease characteristics were similar between treatment arms of the individual studies as well as generally between the studies.

The Sponsor submitted three studies, ABS-AS-102, -202, and -303, in support of broadening the age of use for ProAir RespiClick. All of the studies enrolled children aged 4 and 11 years of age, which is consistent with the proposed treatment indications.

Study ABS-AS-102 was an open-labeled, single-center, single-dose, randomized, two-period crossover study in children ages 4 to 11 years old with persistent asthma. The primary objective of the study was to compare the pharmacokinetic profiles of Albuterol MDPI 180 mcg with ProAir HFA 180 mcg. Given that this was primarily a pharmacokinetic/pharmacodynamic study, and except for its inclusion in the overall discussion of safety, will not be discussed in this review. The reader is referred to the Clinical Pharmacology review by Dr. Ren for a detailed analysis and discussion of Study

ABS-AS-102 and the clinical pharmacology aspects related to the this application as a whole.

Study ABS-AS-202 (Section 5.3.1.1) was a dose-ranging study that evaluated the efficacy of Albuterol MDPI 90 mcg, Albuterol MDPI 180 mcg, ProAir HFA 90 mcg, and ProAir HFA 180 mcg, compared to placebo. These data confirmed the efficacy of albuterol, as both Albuterol MDPI and ProAir HFA formulations, in subjects with asthma compared to placebo. A dose-response relationship within the ProAir HFA treatment arms could be generally appreciated, although not statistically significant. There were no appreciable dose-dependent differences between the Albuterol MDPI treatment arms. The results from the study demonstrated the efficacy of both albuterol products compared to placebo and also suggest that the two products performed similarly at a clinical level.

Study ABS-AS-303 (Section 5.3.1.2) comprised the primary focus for the safety evaluation, as well as efficacy, given the overall study design, large subject cohorts, and placebo-controlled periods. The study was designed to support the efficacy and safety of Albuterol MDPI at the proposed recommended dosing in children ages 4 to 11 years old who were diagnosed with persistent asthma. These studies demonstrated a clinically meaningful benefit and acceptable safety profile of Albuterol MDPI in patients with persistent asthma at the recommended dosing.

Safety data from Studies ABS-AS-102, -202, and -303 provide the pivotal safety information for Albuterol MDPI in children ages 4 to 11 years old. These three studies, in conjunction with the well known safety profile of inhaled albuterol and the recently approved Albuterol MDPI device in patients ages 12 years and older, allows for adequate analyses to identify potential safety signals.



## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Clinical Studies Included in the Assessment of Efficacy

#### 5.3.1.1 ABS-AS-202

Study ABS-AS-202, entitled “A Single-Dose, Multicenter, 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”, was conducted between July 11, 2013 and October 9, 2013. This was designed as a phase 2 multicenter, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 5-treatment, 5-period, 10-sequence, 5-way crossover study in pediatric patients aged 4-11 years old with persistent asthma.

Patients were randomly allocated to 1 of 10 sequences containing the following 5 treatment arms:

- Treatment A: Albuterol MDPI 90 mcg, single dose
- Treatment B: Albuterol MDPI 180 mcg, single dose
- Treatment C: ProAir HFA 90 mcg, single dose
- Treatment D: ProAir HFA 180 mcg, single dose
- Treatment E: Placebo MDPI + Placebo ProAir HFA, single dose

Treatments were administered in a double-blind manner to eliminate any potential observer and/or patient bias. The placebo control was chosen to provide a way of demonstrating the safety and efficacy of study drug by showing the difference between active drug and placebo.

The study consisted of three periods with seven subject visits. Following an initial screening visit, subjects entered a 16-day Run-in Period prior to their first treatment visit. During the Treatment Period, subjects had five visits followed by a final visit prior to completion of the study. All subjects underwent treatment washout from protocol-prohibited medications prior to the screening visit. During the 16-day Run-in Period, subjects continued their inhaled corticosteroid maintenance asthma treatment and recorded their morning peak expiratory flow (PEF) measurements in a daily diary. Following randomization, subjects self-administered the study medication at their assigned study site for each of the five Treatment Periods. Eligible subjects were randomized to receive each of the five treatments on separate occasions with each treatment administered in a double-blinded, double-dummy manner such that for each treatment, subjects received a single actuation from each of four inhalers in a combination comprising two Albuterol MDPI inhalers and two ProAir HFA inhalers. A three to seven day washout period was completed after each Treatment Period.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
  - Male or female subjects aged 4-11 years of age
  - Documented physician diagnosis of persistent asthma of  $\geq 6$ -months duration that was stable for  $\geq 4$ -weeks prior to the screening visit. The asthma diagnosis was in accordance with the National Asthma Education and Prevention Program Guidelines Expert Panel Report 3 (EPR3)
  - Able to self-perform spirometry reproducibly
  - FEV<sub>1</sub> 60 to 90% predicted for age, height, and sex
  - Demonstrated reversible bronchoconstriction as verified by a  $\geq 15\%$  increase in baseline FEV<sub>1</sub> within 30 minutes following inhalation of 180 mcg of albuterol
  - Was maintained on stable low-dose inhaled corticosteroids, leukotriene modifiers, inhaled cromones, or on  $\beta 2$ -agonists alone as needed
  
- Major Exclusion Criteria
  - History of life-threatening asthma defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures
  - Any asthma exacerbation requiring oral corticosteroids within 3 months of the screening visit or any asthma-related hospitalization 6-months prior to the screening visit
  - History or current of respiratory infection or disorder within 14 days preceding the screening visit
  - History or current evidence of any concurrent medical disorder
  - Use of any protocol-prohibited medications

Subjects were permitted to receive the following medications during the washout periods provided the prescribed dosing was stable for four weeks prior to the screening visits. These medications were withheld as pre-specified prior to and throughout the treatment day

- Inhaled corticosteroids
- ProAir HFA (as rescue medication)
- Leukotriene modifiers

- Cromolyn
- Nedocromil

The primary efficacy endpoint of the study was the baseline-adjusted percent-predicted FEV<sub>1</sub> versus time curve over six hours after dosing (PPFEV<sub>1</sub> AUC<sub>0-6</sub> [%\*hour]). The primary statistical analysis was the mixed-effect ANOVA with fixed effects of baseline FEV<sub>1</sub>, sequence, treatment (device) group, period, site, and random effect for subject within sequence. Comparisons of the mean difference between each active group and placebo at each dose level were analyzed for the primary efficacy variable with the comparison of interest being tested at the two-sided 0.05 significance level in a sequential manner as follows: Albuterol MDPI 180 mcg vs. placebo; Albuterol MDPI 90 mcg vs. placebo, ProAir HFA 180 mcg vs. placebo; and ProAir HFA 90 mcg vs. placebo. If a test was not significant at this level then no further testing was performed. The mixed model was used to provide estimates with 95% CI of treatment means and the difference of active treatment means with placebo. A full discussion of the statistical analyses can be found in the Office of Biostatistics review by Yu Wang, PhD.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1. Only treatment emergent adverse events were included in summaries, while, all adverse events (non-treatment emergent and treatment emergent) were listed. Adverse events with an onset on the day of treatment were assigned to the treatment given on that day. Summaries of incidence rates, intensity, and relationship to study drug of individual adverse events by System Organ Class and Preferred Term were prepared. Each subject was counted only once within each preferred term. Counts of adverse events by maximum intensity were presented for subjects in the Safety Population by treatment group. The analysis of adverse event intensity was by maximum intensity by term by subject; therefore, a subject could be counted more than once among the intensity categories. Similarly, counts of adverse events by strongest relationship to study drug were presented. No statistical tests were performed. If a subject reported more

than one adverse event within a preferred term, only the adverse event with the strongest relationship or the greatest intensity, as appropriate, was included in the summaries of relationship and intensity. Summaries of incidence rates of adverse events leading to withdrawal and of serious adverse events were produced. No statistical tests were performed. If applicable, data listings of adverse events leading to withdrawal and of serious adverse events were also included.

A total of 61 subjects were randomized at 14 study sites throughout the US. Subject Of the 61 subjects who received  $\geq 1$  dose of study drug, 57 completed the study. All four of the subjects who discontinued the study did so for "other reason" and not due to death or adverse event. Of the 4 patients who discontinued the study, the last treatment received was placebo in Period 2, Albuterol MDPI 90 mcg in Period 3, Albuterol MDPI 180 mcg in Period 3, and Albuterol MDPI 180 mcg in Period 5.

The Full Analysis Set included all randomized subjects in the Intent-to-Treat population who received  $\geq 1$  dose of randomized study drug and had  $\geq 1$  post-baseline assessment and was used as the population to test the primary efficacy endpoint. This population was used for the primary efficacy analysis. The Safety population included all randomized subjects who received  $\geq 1$  dose of randomized study drug. The Per-Protocol population included all data from randomized subjects obtained prior to a major protocol violation, if any.

The largest number of incomplete assessments was five of 61 in Period 1 during which three subjects treated with Albuterol MDPI 180 mcg and two subjects treated with Albuterol MDPI 90 mcg had incomplete assessments. In Period 2, one of the 60 subjects treated with Albuterol MDPI 180 mcg and one subject treated with ProAir HFA 90 mcg had incomplete assessments. In Period 3, two of the subjects treated with Placebo had incomplete assessments. All 58 assessments during Period 4 were completed. In Period 5 where there were a total of 57 assessments with one placebo-

treated subjects having an incomplete assessment. There were no amendments made to the protocol.

There were a total of five major protocol violations that occurred during the 305 dosing sessions. Four of the protocol violations involved inclusion criteria and one was due to noncompliance with study medication. All five subjects were allowed to continue in the study. The overall number and type of protocol violations were similar across study arms and are not expected to affect the interpretation of the results.

All children were age 4 to 11 years with the average subject being approximately 9 years of age, male (38 males; 23 females) and approximately equal numbers of Blacks (n=29) and Whites (n=28). Only three patients between the ages of 12 to 18 years of age were randomized in the study. All subjects had persistent asthma for  $\geq 6$  months that had been medically stable for  $\geq 4$  weeks prior to screening. Given the small group size, there was some disparity between treatment groups regarding various characteristics, e.g., one treatment group was all black and another treatment group was all male. Overall, the subject demographics and distribution is not believed to adversely affect the interpretation of the results from this study.

#### 5.3.1.2 ABS-AS-303

Study ABS-AS-301, entitled “*A Three-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Chronic-Dose Safety and Efficacy Study of Albuterol Multi-Dose Dry Powder Inhaler (MDPI) Relative to Placebo in Pediatric Asthmatics*”, was conducted between June 10, 2014 and February 11, 2015. The study was designed as a three-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of Albuterol MDPI compared to Placebo MDPI in children 4 to 11 years old with persistent asthma. The primary objective of the study was to assess the overall efficacy and safety of Albuterol administered via MDPI compared to Placebo over a 3-week period in subjects diagnosed with persistent

asthma.

The study consisted of three periods: a screening/run-in period up to 14 days; Treatment period of three weeks (Treatment Day 1 to Treatment Day 22); and a telephone follow-up approximately 25 days after the first dose of study drug.

Subjects with asthma requiring maintenance treatment on inhaled corticosteroids ( $\leq 200$  mcg of fluticasone propionate per day or equivalent), leukotriene modifiers, or inhaled cromones, could be enrolled in the study if the regimens were stable for  $\geq 4$  weeks prior to the screening visit. The subject's asthma had to be manageable for the duration of the study and all subjects were provided and permitted to use study rescue medication (i.e., ProAir HFA) as needed for the treatment of acute asthma symptoms. Subjects were required to adhere to washout requirements and meet the spirometry requirements prior to entering the single-blind run-in period. During the run-in period, subjects continued using their current asthma therapy and single-blind placebo MDPI.

Subjects who met the randomization criteria were randomly assigned to one of two treatment arms in a 1:1 ratio as follows:

- Albuterol MDPI 180 mcg QID
- Placebo MDPI QID

Subjects' parent/guardian recorded nocturnal awakenings due to asthma, pre-morning dose peak expiratory flow, daytime asthma symptoms score, rescue and study medication use, and concomitant medication usage every day prior to their morning medications.

During the study visits on Treatment Days 1 and 22, pulmonary function testing consisting of serial FEV1 and serial peak expiratory flow was assessed. Predose baseline spirometry was obtained before administration of study drug at each visit.

Safety was monitored by reviewing the occurrence of adverse events, physical examinations, vital signs assessments, and 12-lead ECG within 15 minutes prior to dosing and approximately 60 minutes after completion of dosing. Subjects terminating early completed the Treatment Day 22 and follow-up safety procedures.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
  - Male or female subjects aged 4 to 11 years
  - Documented diagnosis of asthma per EPR3 Guidelines for  $\geq 6$  months duration that had been stable for  $\geq 4$  weeks prior to the screening visit
  - FEV<sub>1</sub> 50 to 95% predicted for age, height, and gender at the screening visit following  $\geq 6$  hour period without  $\beta_2$ -agonist use
  - Use of inhaled corticosteroids for persistent asthma at a stable, low to medium dose for  $\geq 4$  weeks (defined as the equivalent of  $\leq 200$  mcg/day of fluticasone propionate), leukotriene modifiers, inhaled cromones, and/or SABA as needed
  - Able to perform acceptable and reproducible PEF measurements
  - Demonstration of reversible bronchoconstriction consisting of  $\geq 15\%$  increase from baseline FEV<sub>1</sub> within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA
- Major Exclusion Criteria
  - History of life-threatening asthma defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures
  - Any asthma exacerbation requiring oral corticosteroids within 3 months of the screening visit or any asthma-related hospitalization 6-months prior to the screening visit
  - History or current of respiratory infection or disorder within 28 days preceding the screening visit
  - History or current evidence of any concurrent medical disorder
  - Use of any protocol-prohibited medications

The primary efficacy endpoint of the study was the baseline-adjusted percent-predicted FEV<sub>1</sub> versus time curve over six hours after dosing (PPFEV<sub>1</sub> AUC<sub>0-6</sub>) over the three-week treatment period using the Full Analysis Set, which included all randomized

subjects in the Intent-to-Treat population who received  $\geq 1$  dose of randomized study drug and had  $\geq 1$  post-baseline assessment and was used as the population to test the primary efficacy endpoint. The primary statistical analysis was the mixed-model repeated-measures analysis with baseline-adjusted FEV<sub>1</sub> AUEC<sub>0-6</sub> over the 3-week treatment period as the response, fixed effects of pooled center, treatment group, study day, and study day by treatment interaction with baseline measured at each study day as a covariate. Rejection of the null hypothesis at the 0.05 level of significance and a positive difference in the least squares means was considered to be a successful demonstration of efficacy. The mixed model was used to provide estimates with 95% CI of treatment means and the difference of the active treatment mean with placebo. A full discussion of the statistical analyses can be found in Dr. Wang's review.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1. Only treatment emergent adverse events were included in summaries, while, all adverse events (non-treatment emergent and treatment emergent) were listed. Adverse events with an onset on the day of treatment were assigned to the treatment given on that day. Summaries of incidence rates, intensity, and relationship to study drug of individual adverse events by System Organ Class and Preferred Term were prepared. Each subject was counted only once within each preferred term. Counts of adverse events by maximum intensity were presented for subjects in the Safety Population by treatment group. The analysis of adverse events intensity was by maximum intensity by term by subject; therefore, a subject could be counted more than once among the intensity categories. Similarly, counts of adverse events by strongest relationship to study drug were presented. No statistical tests were performed. If a subject reported more than one adverse event within a preferred term, only the adverse event with the strongest relationship or the greatest intensity, as appropriate, was included in the summaries of relationship and intensity. Summaries of incidence rates of adverse events leading to withdrawal and of serious adverse events were produced. No



statistical tests were performed. If applicable, data listings of adverse events leading to withdrawal and of serious adverse events were also included.

There was one amendment made to the protocol that largely detailed clarifications to protocol procedures. Overall, the protocol amendments did not change the interpretability of the study or negatively impact the safety of the subjects enrolled in the study.

A total of 211 subjects were initially enrolled and entered into the Run-in Period of the study; however, 25 of these subjects were not randomized due to failing randomization criteria. Consequently, 186 subjects were randomized at 32 study sites throughout the US to receive study drug with 92 subjects randomized to Placebo MDPI and 94 Subjects to Albuterol MDPI. One subject randomized to the Albuterol MDPI treatment arm was not treated, therefore the Safety Population consisted of 185 subjects. The Full Analysis Set consisted of 184 subjects. A total of 24 (13%) subjects discontinued the study: 14 subjects from the Albuterol MDPI arm and 10 from the placebo treatment arm. "Other reasons" was the most common reason reported for discontinuation from the study including 5 subjects from each treatment arm. No subjects were discontinued from the study due to death or adverse event.

There were 7 (4%) subjects with  $\geq 1$  protocol violations:

- Placebo MDPI treatment arm (n=3)
  - excluded concomitant medication (n=1)
  - failure to sign ICF (n=1)
  - noncompliance to study medication (n=1)
- Albuterol MDPI treatment arm (n=4)
  - failure to meet inclusion criteria (n=2)
  - failure to sign ICF (n=1)

- excluded concomitant medication (n=1)

One placebo-treated subject (#12482023) was discontinued from the study due to noncompliance with inhalers and diary data, two subjects were discontinued for excluded concomitant medication, specifically due to corticosteroid usage for asthma exacerbation (one subject from each treatment arm), and two Albuterol MDPI-treated subjects were discontinued due to inclusion criteria violations.

The overall number and type of protocol violations were similar across study arms and are not expected to affect the interpretation of the results.

Overall, the baseline demographics and disease characteristics were similar between treatment arms with the average patient being approximately 8.5 years of age (range 4-11 years) with 25% of placebo MDPI subjects and 32% of Albuterol subjects being between the ages of 4 to 7 years old. There was almost an equal number of Black and White patients randomized (54% and 44%, respectively) and with a greater proportion of males than females (58% versus 43%, respectively). All subjects carried a diagnosis of persistent asthma and baseline FEV<sub>1</sub> were comparable between treatment arms.

## 6 Review of Efficacy

### **Efficacy Summary**

In the initial NDA submission, the Sponsor aimed to develop Albuterol MDPI to be comparable to ProAir HFA such that both products delivered equivalent 90 mcg doses of albuterol base per device actuation with the intent that Albuterol MDPI could be dosed in the same manner as ProAir HFA.

Although not strictly designed to analyze for non-inferiority or comparability, the data from Studies ABS-AS-102 and -202 demonstrated similar single-dose efficacy and safety profiles of Albuterol MDPI and ProAir HFA in subjects age 4 to 11 years of age who were diagnosed with persistent asthma. Both studies met their primary endpoints assessing FEV<sub>1</sub> and analysis of the pharmacodynamic and pharmacokinetic parameters further supported a high degree of clinical similarity between Albuterol MDPI and ProAir HFA at each of the five doses tested. Additional analysis of the data did not demonstrate a difference in the onset of action of albuterol between either of the two products. Taken together, the current studies support the Sponsor's proposed dosing of Albuterol MDPI up to 180 mcg in subjects ages 4 years and older.

Study ABS-AS-303 met its primary endpoint demonstrating that subjects treated with Albuterol-MDPI 180 mcg experienced clinically meaningful and statistically significant increases in  $\Delta$ FEV<sub>1</sub> AUC<sub>0-6hr</sub> compared to placebo-treated subjects over the 3-weeks of the controlled period of the studies. Analyses of the secondary endpoints of the study were supportive and together the data confirm the known effectiveness of albuterol in subjects with asthma.

Of note, the Sponsor is seeking to extend the claim of treatment of exercise-induced bronchospasm in patients age 4 to 11 years old based on extrapolation of the clinical

data presented in the current submission and that demonstrated in their initial NDA for ProAir RespiClick, which demonstrated a clinical benefit in subjects with exercise-induced bronchospasm 12 years of age and older. Overall, the data support the claim that pharmacologic therapy with Albuterol MDPI 180 mcg effectively treats and prevents bronchospasm in patients 4 years of age and older who are diagnosed with persistent asthma and/or exercise-induced asthma.

## **6.1 Indication**

The Sponsor has proposed the following two indications for Albuterol MDPI:

- Treatment and 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

### **6.1.1 Methods**

As discussed in Section 5.2, data from studies ABS-AS-102, -202, and -303 were used to support the efficacy of Albuterol MDPI for treating patients with persistent asthma in subjects 4 to 11 years of age. These three studies were well-designed and adequately conducted to provide sufficient evidence to demonstrate a clinically meaningful benefit of Albuterol MDPI in patients with reversible obstructive airway disease and to extrapolate the data to include patients with exercise-induced bronchospasm.

### **6.1.2 Demographics**

Baseline demographics and disease characteristics for each of the clinical studies used to evaluate efficacy are included in the discussion of the individual studies (Section 5.3). Overall, each of the individual studies subjects' baseline demographics and disease characteristics were generally balanced between treatment arms as well as between the

individual studies. The subject population enrolled in these studies is representative of the targeted patient population for the proposed indications of Albuterol-MDPI.

### 6.1.3 Subject Disposition

Subject disposition for each of the clinical studies used to evaluate efficacy are included in the discussion of the individual studies (Section 5.3). Overall, each of the studies had a high proportion (>90%) of subjects completing the study. For the small number of subjects that did discontinue from the studies, the numbers of subjects and reasons for discontinuation were similar between treatment arms with the most frequent reason reported as “other reason”. On the whole, the patterns of subject disposition did not appear to favor or disfavor those who were randomized to receive Albuterol-MDPI.

### 6.1.4 Analysis of Primary Endpoint

#### 6.1.4.1 Study ABS-AS-202

The primary efficacy endpoint of Study ABS-AS-202 was the baseline-adjusted percent-predicted FEV<sub>1</sub> versus time curve over six hours after dosing (PPFEV<sub>1</sub> AUC<sub>0-6</sub> [%\*hour]) for the five treatment groups. Subjects treated with any dose of Albuterol MDPI or ProAir HFA demonstrated significant increases in  $\Delta$ FEV<sub>1</sub> AUC<sub>0-6hr</sub> compared to placebo-treated subjects (Table 3). There were no differences between Albuterol MDPI 90 mcg and 180 mcg, however, there was a significant difference between the two ProAir HFA doses. The differences between doses do not represent a clinically meaningful difference, and most importantly, each of the doses of Albuterol MDPI were effective and similar to that of the ProAir HFA 180 mcg dose, demonstrating maximal effect at either dose. These data demonstrate a clinical benefit for the use of albuterol, delivered via MDPI or HFA, in subjects with persistent asthma.

**Table 3. Study ABS-AS-202:  $\Delta$  PPFEV<sub>1</sub> AUC<sub>0-6hr</sub>\* (Full Analysis Set)**

<b>Treatment Arm</b>	<b><math>\Delta</math>AUC<sub>0-6hr</sub> L*hr Mean<math>\pm</math>SE (95% CI) (N)</b>	<b>Treatment Difference Drug-Placebo Mean<math>\pm</math>SE (95% CI) (p-value)</b>
<b>Placebo</b>	25 $\pm$ 6 (13, 38) (59)	-
<b>Albuterol-MDPI 90 mcg</b>	47 $\pm$ 6 (34, 59) (58)	21 $\pm$ 5 (12, 31) (<0.0001)
<b>ProAir-HFA 90 mcg</b>	38 $\pm$ 6 (25, 50) (59)	13 $\pm$ 5 (3, 22) (0.01)
<b>Albuterol-MDPI 180 mcg</b>	48 $\pm$ 6 (36, 60) (59)	23 $\pm$ 5 (13, 32) (<.0001)
<b>ProAir-HFA 180 mcg</b>	49 $\pm$ 6 (37, 62) (59)	24 $\pm$ 5 (14, 33) (<.0001)
*source: Adapted from the Sponsor's ABS-AS-202 Study Report, Table 9		

#### 6.1.4.3 Study ABS-AS-303

The primary efficacy endpoint of Study ABS-AS-303 was the baseline-adjusted percent-predicted FEV<sub>1</sub> versus time curve over six hours after dosing (PPFEV<sub>1</sub> AUC<sub>0-6</sub>) over the three-week treatment period using the Full Analysis Set (Table 4). Albuterol-MDPI-treated subjects demonstrated an increase of 25%\*hr compared to Placebo-MDPI-Treated subjects over the 3-week treatment period. These data represent a clinically meaningful effect for subjects age 4 to 11 years old with persistent asthma treated with Albuterol-MDPI 180 mcg compared to placebo-treated subjects.

**Table 4. Study ABS-AS-303:  $\Delta$ PPFEV<sub>1</sub> AUC<sub>0-6hr</sub> Over 3 Weeks (Full Analysis Set)**

Study 303	$\Delta$ PPFEV <sub>1</sub> AUC <sub>0-6hr</sub> (%*hr)		Treatment Difference Mean $\pm$ SE (95% CI) (p-value)
	Albuterol-MDPI 180 mcg Mean $\pm$ SE (95% CI) (n)	PBO Mean $\pm$ SE (95% CI) (n)	
LS mean	44 $\pm$ 3 (37, 50) (92)	19 $\pm$ 3 (12, 25) (92)	25 $\pm$ 5 (16, 34) (<0.0001)
*source: Adapted from the Sponsor's ABS-AS-303 Study Report, Table 11 LS: least square			

### 6.1.5 Analysis of Secondary Endpoints(s)

#### 6.1.5.1 Study ABS-AS-202

Analyses of the secondary efficacy endpoints fully supported the results of the primary efficacy measure (data not shown). Analyses regarding time to onset of action was also explored and demonstrated no significant difference in the time to onset between Albuterol-MDPI and ProAir-HFA (Table 5). The reviewer is referred to Dr. Wang's review for a detailed discussion of the secondary endpoints for Study ABS-AS-202.

**Table 5. Time in Minutes to 15% Response Among Responders (Full Analysis Set)**

Treatment Arm	Time (min) to Onset Mean $\pm$ SE (n)
Albuterol-MDPI 90 mcg	11 $\pm$ 5 (26)
ProAir-HFA 90 mcg	10 $\pm$ 7 (27)
Albuterol-MDPI 180 mcg	9 $\pm$ 5 (22)
ProAir-HFA 180 mcg	13 $\pm$ 8 (24)
*source: Adapted from the Sponsor's ABS-AS-202 Study Report, Table 13	

### 6.1.5.2 Study ABS-AS-303

Analyses of the secondary efficacy endpoints fully supported the results of the primary efficacy measure. As shown in Table 6, the peak effort flow rate  $AUC_{0-6hr}$  over the three-week treatment period demonstrated a significant difference of 76 L/min\*hr in favor of Albuterol-MDPI compared to Placebo-MDPI over the 3-week controlled.

**Table 6. Baseline Adjusted PEF  $AUC_{0-6hr}$  (L/min\*hr) Over 3 Weeks (Full Analysis Set)**

Study 303	$\Delta PPF_{EV_1} AUC_{0-6hr}$ (%*hr)		Treatment Difference Mean $\pm$ SE (95% CI) (p-value)
	Albuterol-MDPI 180 mcg Mean $\pm$ SE (95% CI) (n)	PBO Mean $\pm$ SE (95% CI) (n)	
<b>LS mean</b>	148 $\pm$ 10 (128, 168) (92)	72 $\pm$ 10 (51, 92) (92)	76 $\pm$ 14 (48,105) ( $<0.0001$ )
*source: Adapted from the Sponsor's ABS-AS-303 Study Report, Table 12 LS: least square			

### 6.1.7 Subpopulations

No subgroup analyses were planned or conducted during Study ABS-AS-202. Study ABS-AS-303 was not powered to detect differences in treatment efficacy for subgroups, however, summary statistics were calculated using the Full Analysis Set based on sex, age group (4-7 years and 8-11 years) and by race (White vs. non-White). No significant subgroup effects on efficacy were seen based on sex, race, or age group. The reader is referred to Dr. Wang's statistical review for a detailed analysis of these endpoints.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Albuterol is known to be a safe and effect treatment for patients with bronchospasm. As discussed above, the proposed dose of Albuterol-MDPI was fully assessed in the



Sponsor's clinical program and found to be safe and effective using the new MDPI device. Therefore, approval of Albuterol-MDPI 180 mcg for the treatment and short-term prevention of reversible airway obstruction and for the prevention of exercise-induced bronchospasm is acceptable.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The reader is referred to Dr. Wang's statistical review for a discussion of persistence of efficacy.

#### 6.1.10 Additional Efficacy Issues/Analyses

The reader is referred to Dr. Wang's statistical review for a discussion of additional efficacy issues and analyses.

## 7 Review of Safety

### **Safety Summary**

Albuterol has been in clinical use in the USA for over 30-years as a treatment for patients with acute asthma and as prophylaxis for exercise-induced bronchospasm. Consequently, the efficacy and safety of albuterol are well understood. Inhalation is the preferred route of delivery for patients with bronchospasm as it rapidly delivers a relatively low but effective dose of drug to the site of action. An added advantage of inhalation delivery is that the drug largely bypasses issues from drug metabolism and avoids many of the complications of systemic side effects. The safety review for the original NDA 205636 included a total of ten clinical studies in adult and adolescent patients and supported the overall safety of Albuterol MDPI. The safety data submitted in this sNDA will only include data from the three pediatric studies ABS-AS-102, -202, and -303 (Table 2).

During the approval of the adolescent and adult indication, the Agency required the Sponsor to change the product labeling to reflect the administered dose of Albuterol MDPI to the metered dose (b) (4). Therefore, discussion in this review relates to the 90 mcg-emitted dose of Albuterol MDPI, which corresponds to a metered dose of 97 mcg.

No deaths, serious adverse events, or discontinuations occurred during Studies ABS-AS-102, -202, and -303, although two subjects reported a serious adverse event during the placebo run-in period of Study ABS-AS-303. In general, the percentage of subjects reporting adverse events was either similar between treatment arms or slightly greater in placebo-treated subjects. Headache was the most commonly reported adverse event reported in  $\geq 2\%$  of subjects and greater in the Albuterol MDPI treatment arm.

Overall, analysis of the safety data did not demonstrate an important safety signal with the use of Albuterol MDPI and the results support the safety of Albuterol MDPI in the treatment or prevention of bronchospasm in patients 4 years of age and older with obstructive airway disease.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from Study ABS-AS-303 provides the pivotal safety information for Albuterol MDPI in children ages 4 to 11 years of age. The study was designed to include a 3-week double-blind treatment period utilizing the MDPI device proposed for marketing. This study allows for the direct comparison between treatment and placebo allowing for a more complete evaluation of potential safety signals with Albuterol MDPI.

As described in Section 5, Study ABS-AS-303 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group studies in subjects aged 4 to 11 years old with persistent asthma who were on stable doses of inhaled corticosteroids. Subjects were randomized 1:1 to either Albuterol MDPI 180 mcg QID or Placebo MDPI QID for 3-weeks.

Supportive safety data are provided from Studies ABS-AS-102 and -202 and will be discussed separately from the pooled analyses in the relevant safety sections.

Study ABS-AS-102 was a phase 1, single-center, randomized, open-label, single-dose, two-period crossover study in children ages 4 to 11 years old with persistent asthma. The primary objective of the study was to compare the PK profiles of Abluterol MDPI 180 mcg to ProAir HFA 180 mcg.

Study ABS-AS-202 was designed as a multicenter, randomized, double-blind, double-dummy, single-dose, five-treatment, five-period, 10-sequence, placebo-controlled,

crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in children ages 4 to 11 years old with persistent asthma.

### 7.1.2 Categorization of Adverse Events

All subjects were asked at each contact as to whether any adverse events were experienced since their previous visit. An adverse event was defined as “*any untoward medical occurrence in a clinical trial patient that developed or worsened in severity during the conduct of the clinical study of a pharmaceutical product and did not necessarily have a causal relationship to the study drug*”. An adverse event could, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product. Events occurring prior to randomization were considered to be non-treatment-emergent adverse events and those occurring post-randomization as treatment-emergent adverse events.

The onset and end dates, duration, action(s) taken regarding study drug, treatment administered, and outcome for each adverse event were recorded. The intensity or severity of each adverse event was characterized as mild, moderate, or severe.

A serious adverse event was defined as an adverse event that resulted in any of the following:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- A congenital abnormality or birth defect
- An important medical event which required medical intervention to prevent any of the above outcomes. Any suspected transmission of an infectious agent via a medicinal product was considered an important medical event

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. An asthma exacerbation was not considered an adverse event unless it met the criteria for a serious adverse event. Thus, once an asthma exacerbation met the criteria for serious, it was considered to be an adverse event and it was reported as both an adverse event and serious adverse event. All cases of asthma exacerbation were assessed separately.

Clinical laboratory testing was not considered a primary safety concern in Study ABS-AS-303 since the systemic exposure to albuterol after inhalation administration is known to be low. Furthermore, prior studies of albuterol have demonstrated only minor effects on most laboratory parameters, except occasionally on elevated serum potassium and blood glucose levels. Laboratory parameters were assessed in Study ABS-AS-102 at screening and at the final treatment visits. In Study ABS-AS-202, laboratory evaluations were only performed at the screening visit and at baseline; consequently, the results will not be discussed in the current review. When clinical laboratory evaluations were conducted they included the following measures:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count, mean cell hemoglobin, mean cell volume, and mean cell hemoglobin concentration
- Serum chemistry: sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, inorganic phosphorus, glucose, blood urea nitrogen, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), albumin, total protein, total bilirubin, and lactate dehydrogenase
- Urinalysis: protein, glucose, ketones, blood, pH, bilirubin, and leukocytes

Vital signs, physical exams, and ECG recordings were performed for all three studies by the principle investigator at the screening visit, baseline visit, and/or during treatment visits.

## **7.2 Adequacy of Safety Assessments**

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

### **7.2.2 Explorations for Dose Response**

The current submission provided limited data to analyze for a dose-dependent relationship of adverse events using therapeutic doses of Albuterol MDPI. Review of Study ABS-AS-202, which administered doses of Albuterol MDPI 90 mcg and 180 mcg, did not demonstrate a clear correlation between drug dose and increased adverse events. In summary, analysis of the limited data did not demonstrate a clear dose-response relationship regarding the increased frequency of adverse events was not observed.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

No direct analyses were performed regarding the administration of Albuterol MDPI and the occurrence of adverse events as related to metabolism, clearance, or interaction of the active drug. The reader is referred to the clinical pharmacology review by Dr. Ren for further discussion of Albuterol MDPI metabolism, clearance, and drug interaction.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

No deaths were reported in any of the clinical studies used to support this application.

### 7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during the controlled period of Study ABS-AS-303; however, two serious adverse events were reported during the placebo run-in period:

- Subject 12492004 was a 7-year-old Black male diagnosed with pneumonia who was treated and had complete resolution. He was subsequently discontinued from the study.
- Subject 12480009 was a 7-year-old White female who reportedly developed an “emotional disorder” during the single-blind, placebo run-in period. Despite the ongoing event, she was randomized to the Albuterol MDPI treatment arm but was ultimately need to be discontinued from the study.

No serious adverse events were reported in Studies ABS-AS-102 or -202.

In summary, the only serious adverse events reported occurred during the placebo run-in period of Study ABS-AS-303. No serious adverse events were reported during the treatment periods of the studies. Overall, these data do not identify a new safety signal associated with the use of Albuterol MDPI.

### 7.3.3 Dropouts and/or Discontinuations

There were no adverse events leading to discontinuation from any of the studies.

### 7.3.4 Significant Adverse Events

The Sponsor performed additional analyses assessing adverse events potentially associated with the use of  $\beta_2$ -agonists including cardiovascular metabolic, and central nervous system effects. To assess the possible association between these effects, the Sponsor evaluated all adverse events within the cardiac disorders, central nervous system, and vascular disorders System Organ Classes in conjunction with related

preferred terms from the metabolism and nutritional disorders, psychiatric disorders, general conditions, and administrative disorders investigations, and musculoskeletal System Organ Classes.

No evidence of  $\beta_2$ -agonists-associated adverse effects were contributed to Albuterol MDPI treatment in children except for headache, which was reported in equal proportions between Placebo MDPI-treated and Albuterol MDPI-treated subjects. Three subjects treated with ProAir HFA 90 mcg reported headache compared to none in the Albuterol MDPI treatment arm of Study ABS-AS-202. Similarly, three Albuterol MDPI-treated subjects versus four Placebo MDPI-treated subjects in Study ABS-AS-303 reported headache.

Hypersensitivity reactions have been reported following the administration of albuterol sulfate presenting as urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. In Study ABS-AS-202, one subject treated with Albuterol MDPI 180 mcg reported an adverse reaction of urticaria. Similarly low levels of hypersensitivity reactions were observed during Study ABA-AS-303 with one Placebo MDPI-treated subject reporting a rash of moderate severity lasting one week. Two Albuterol MDPI subjects reported potential hypersensitivity related reactions including one case of erythema and a second subject reporting eye pruritis, skin pruritis, and urticaria of mild severity that lasted approximately one day. Given that the Placebo MDPI device contained lactose, and that lactulose containing products are known to cause anaphylaxis in some people with severe hypersensitivity to milk proteins, a statement regarding anaphylaxis should be included in the product label.



## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

A total of 21 (23%) Albuterol MDPI-treated subjects reported an adverse event compared to 21 (23%) Placebo MDPI-treated subjects during the 3-week controlled period of Study ABS-AS-303 (Table 7). All of the adverse events in both treatment arms were reported as mild or moderate in intensity. Overall, there were no clinically important differences between study arms regarding the types or frequency of adverse events.

**Table 7. Summary of Adverse Events in Study ABS-AS-303 Occurring in  $\geq 2\%$  of Subjects in Albuterol MDPI Treated Subject and Greater than Placebo MDPI Treated Subjects by MedDRA System (ITT)**

Category	Number (%) of Patients	
	Albuterol MDPI N 93	Placebo MDPI N 92
<b>Patients <math>\geq 1</math> Adverse Event</b>	21 (23)	21 (23)
<b>Discontinuations due to AE</b>	1 (<1)*	0
<b>Gastrointestinal disorders</b>		
Vomiting	3 (3)	1 (1)
<b>Infections and infestations</b>		
Nasopharyngitis	2 (2)	1 (1)
<b>Respiratory, thoracic, &amp; mediastinal disorders</b>		
Oropharyngeal pain	2 (2)	1 (1)
MDPI: multipledose dry powder inha er; source: ISS, Table 9. *Discontinuation occurred during the placebo run-in period		

The most common adverse events were reported in the gastrointestinal disorders System Organ Classes with a greater proportion of Albuterol MDPI-treated subjects reporting vomiting compared to Placebo MDPI-treated subjects (3% vs. 1%).

The most frequently reported adverse event during Study ABS-AS-202 was headache, which was reported by three (5%) subjects treated with ProAir HFA 90 mcg. There were no other adverse events that occurred in greater than one patient (data not shown).

#### 7.4.2 Laboratory Findings

Clinical laboratory tests were performed at baseline and the end of Study ABS-AS-102. Overall, laboratory tests showed no clinically meaningful trends in mean changes from baseline (data not shown). Small differences were noted in the mean values at each time point in serum chemistry, hematology, and urinalysis, although the vast majority of values remained within normal range (data not shown).

As agreed upon previously with the Agency, Studies ABS-AS-202 and --303 only collected clinical laboratory tests at baseline and not after dosing; therefore, no conclusions can be drawn regarding drug effect on clinical laboratories.

Overall, the data available did not identify a clinically significant signal regarding changes in laboratory values in subjects treated with Albuterol MDPI. These results are consistent with the safety review from the original NDA 205636.

#### 7.4.3 Vital Signs

During Study ABS-AS-102, vital signs were measured at baseline and at 30 minutes and 1, 2, and 6 hours following treatment. Overall, the mean posttreatment values in heart rate, systolic and diastolic blood pressure between the two treatment arms were comparable. A mean increase of 9 and 5 beats/min in heart rate was observed in the Albuterol MDPI and Placebo MDPI treatment arms, respectively, six hours after dosing. For Study ABS-AS-202, vital signs were measured at baseline and at 30 minutes, 1 hour and 4 hours after treatment in each time period. There were no clinically meaningful changes in mean serial values or changes from baseline for any vital signs after treatment with any of the 5 study drugs.

For Study ABS-As-303, vital signs were measured at baseline and 60-minutes after dosing on Treatment Days 1 and 22. As expected, heart rate increased slightly 60-minutes after dosing on both treatment days following Albuterol MDPI administration compared to Placebo MDPI treated subjects. In general there were no clinically meaningful changes observed in blood pressure with either treatment arm at Days 1 and 22. However, potential clinically significant changes in blood pressure were reported in three Placebo MDPI treated subjects and two Albuterol MDPI treated subjects with mild changes in systolic or diastolic blood pressure readings. None of these subjects reported any cardiovascular-related adverse events.

Generally there were no clinically meaningful trends in mean changes from baseline for any vital signs; however, in Study ABS-AS-301 two Albuterol MDPI-treated subjects (increased diastolic blood pressure (n=1), tachycardia (n=1)) and five Placebo MDPI-treated subjects (increased systolic blood pressure (n=2), increased diastolic blood pressure (n=2), and an increase in both systolic and diastolic blood pressure (n=1)) had clinically significant changes in vital signs.

Overall, the changes from baseline in vital signs were small and similar between albuterol treatments (i.e. Albuterol MDPI, ProAir HFA) and not clinically meaningful. These changes are not unexpected given the underlying mechanism of action of albuterol. No new safety signals were identified.

#### 7.4.4 Electrocardiograms (ECGs)

During Study ABS-AS-102, ECGs were collected at the baseline visit and at the study endpoint. One subject shifted from normal at baseline to abnormal at study endpoint due to a clinically nonsignificant abnormal sinus rhythm; and four subjects were abnormal at baseline only. Values throughout the study were comparable for PR, QRS,

QT, and RR interval measurements. No subject had a QT<sub>c</sub> interval length greater than 456 msec at any time point.

A 12-lead ECG was conducted at the screening visit only for Study ABS-AS-202. Only one randomized subject had a clinically significant abnormal ECT at screening that was consistent with a left atrial rhythm and possible biventricular hypertrophy; however, a repeat ECG was performed 48 hours later and interpreted as normal.

Study ABS-AS-303 conducted ECGs at the screening visit, and pre- and post-dose on Treatment Days 1 and 22 within 15 minutes prior to dosing and approximately 60 minutes after completion of dosing. A total of 21 subjects randomized to the Placebo MDPI and 11 Albuterol MDPI-treated subjects had abnormal baseline ECGs. Shifts from normal baseline ECG to abnormal following dosing was reported for five Placebo MDPI-treated subjects compared to six Albuterol MDPI-treated subjects at Treatment Day 1, as well as four and two subjects at Treatment Day 22, respectively. In general, the observed ECG changes were clinically nonsignificant; however, four subjects (two from each treatment arm) demonstrated clinically significant ECG findings. The two Albuterol MDPI subjects and one Placebo MDPI subject had a PR interval greater than 190 msec at both prior and after dosing. One Placebo MDPI subject had a resting heart rate below 50 beats/minute. None of these subjects reported a cardiovascular-related adverse event.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

As discussed in Section 7.2.2, review of the data did not demonstrate a clear dose-response relationship regarding the increased frequency of adverse events at therapeutic levels of Albuterol MDPI.

### **7.5.3 Drug-Demographic Interactions**

No significant subgroup effects on safety were seen based on sex, race, age, or geographic region.

### **7.5.4 Drug-Disease Interactions**

No definitive conclusions can be drawn from the data given the relative good health of the enrolled subjects and the limited amount of placebo-controlled data. In general, no clear drug-disease interaction was identified.

### **7.5.5 Drug-Drug Interactions**

No formal drug interaction studies were conducted with Albuterol MDPI; however, the ProAir HFA package insert notes drug interactions with other short-acting  $\beta_2$ -adrenergic receptor agonists,  $\beta$ -blockers, diuretics, digoxin, and monoamine oxidase inhibitors or tricyclic antidepressants.

## **7.6 Additional Safety Evaluations**

### **7.6.2 Human Reproduction and Pregnancy Data**

There are no adequate and well-controlled studies of Albuterol MDPI or albuterol sulfate in pregnant women. The Sponsor notes that the worldwide marketing experience has reported that various congenital anomalies have been reported in the offspring of

patients treated with albuterol; however, some of these mothers were also taking multiple medications during their pregnancies. No clear pattern of defects has been discerned and a relationship between albuterol use and congenital anomalies has not been established. Animal studies in mice and rabbits have demonstrated evidence of teratogenicity. This reviewer recommends labeling language consistent with the current ProAir HFA labeling and rating of Pregnancy Category C.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No significant effects on safety were seen in children enrolled in the current studies.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose in the current clinical program for Albuterol MDPI. Additionally, there is no indication of any potential for abuse, withdrawal, or rebound of Albuterol MDPI based on data from clinical studies or the scientific literature of orally inhaled  $\beta$ 2-agonists.

## **8 Postmarketing Experience**

Albuterol MDPI was approved on March 31, 2015 in the USA as ProAir RespiClick for use in patients 12 years of age and older. At the time of the current submission no postmarketing data were available.

## **9 Appendices**

### **9.1 Literature Review/References**

None.

### **9.2 Labeling Recommendations**

TBD

### **9.3 Advisory Committee Meeting**

Following the initial review and discussion of the application, the review team determined Albuterol MDPI to be efficacious in children with persistent asthma and/or exercise-induced bronchospasm with an acceptable safety profile and no identifiable serious safety signals or outstanding issues. Consequently, a determination was made deciding that a meeting of the FDA's Arthritis Advisory Committee would not be required.

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KEITH M HULL  
03/24/2016

NIKOLAY P NIKOLOV  
04/04/2016