CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205636
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Submit Date	May 5, 2014
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Division / Office	DPARP/ODE II
Reviewer Name	Keith M Hull, MD, PhD
Review Completion Date	January 28, 2015
Established Name	Albuterol Sulfate
(Proposed) Trade Name	ProAir RespiClick
Therapeutic Class	β_2-adrenergic receptor agonist
Applicant	Teva
Formulation	Multi-dose Dry Powder Inhaler Metered dose: 108 mcg albuterol sulfate Delivered dose: 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 12 years and older

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1 Recommendations/Risk Benefit Assessment

Teva Pharmaceuticals (Sponsor) is submitting a 505(b)(2) New Drug Application (NDA) for Albuterol Multidose Dry Powder Inhaler (Albuterol MDPI) with the proposed tradename *ProAir RespiClick*. 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 12 years of age and older with reversible obstructive airway disease
- prevention of exercise-induced bronchospasm in patients 12 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.

Although not strictly designed to analyze for non-inferiority or comparability, the data from Studies ABS-AS-101 and -201 demonstrated similar single-dose efficacy and safety profiles of Albuterol MDPI and ProAir HFA in subjects age 12 years and older who were diagnosed with persistent asthma. Both studies met their primary endpoints assessing FEV_1 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.

Studies ABS-AS-301 and -304 both met their primary endpoints demonstrating that subjects treated with Albuterol-MDPI 180 mcg experienced clinically meaningful and statistically significant increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ compared to placebo-treated subjects over the 12-weeks of the controlled period of the studies. Analyses of the secondary endpoints of both studies were supportive and together the data confirm the known effectiveness of albuterol in subjects with asthma.

Subjects treated with Albuterol-MDPI 180 mcg in Study ABS-AS-302 demonstrated a significant effect on prevention of exercise-induced bronchospasm compared to subjects treated with Placebo-MDPI. Treatment with Albuterol-MDPI prior to exercise reduced the post-exercise percentage fall in FEV_1 to 6% compared to 22% for placebo-treated subjects. An alternative way to put these findings into perspective is that 84% of Albuterol MDPI-pretreated subjects experienced a <10% decrease in FEV_1 compared to only 16% of placebo-pretreated subjects, which translates into a clinically significant benefit. Together, these data demonstrate a clinically meaningful benefit of Albuterol MDPI 180 mcg for patients diagnosed with exercise-induced bronchospasm.

Studies ABS-AS-307 and -308 were used assess the performance of the new MDPI device. The performance of the MDPI device was a secondary objective in Study ABS-AS-307 and the primary objective of Study ABS-AS-308. The data from these studies demonstrated that the total number of device-related complaints was low and that the proposed MDPI device with integrated counter performed adequately and in a reliable manner with a minimal rate of dose cycle "undercounting".

A total of 10 clinical studies in adult and adolescent patients have been completed and support the safety of Albuterol MDPI. Overall, 1456 patients were included in the clinical program of who 1120 received treatment with Albuterol MDPI. Among patients treated with Albuterol MDPI, 840 were treated with the inhaler proposed for marketing. The primary safety data is derived from clinical studies that were wholly conducted in the USA at geographically diverse locations.

No deaths occurred during the clinical program for Albuterol MDPI. A total of 15 subjects reported serious adverse events which included 13 subjects treated with Albuterol MDPI and two subjects treated with placebo. Similarly, only 10 subjects discontinued a clinical study due to an adverse event (Albuterol MDPI (n=8), Placebo MDPI (n=2)). The majority of the serious adverse events and adverse events resulting in discontinuation were not related to study drug. The most commonly reported adverse events (reported in ≥5% of subjects) included upper respiratory tract infection, nasopharyngitis, and headache. In general, the percentage of subjects reporting adverse events was either similar between treatment arms or slightly greater in placebo-treated subjects. For labeling purposes, adverse events experienced ≥1% of of Albuterol MDPI-treated subjects and greater than placebo-treated subjects was back pain, pain, gastroenteritis, sinus headache, urinary tract infection.

Safety data from Studies ABS-AS-301, -304, and -307 provided the pivotal safety information for Albuterol MDPI. All three studies were designed to include a 12-week double-blind treatment period utilizing the MDPI device proposed for marketing. These studies allow for the direct comparison between treatment and placebo allowing for a more complete evaluation of potential safety signals with Albuterol MDPI. Supportive safety data are provided from Studies ABS-AS-101, -201, -302, and -308, which will be discussed separately from the pooled analyses in the relevant safety sections.

(b) (4)

Together, these studies demonstrated that therapy with Albuterol MDPI 180 mcg effectively treats or prevents bronchospasm in patients 12 years of age and older who are diagnosed with persistent asthma and/or exercise-induced asthma. 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 for use in the proposed patient population.

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

2.1 Product Information

Albuterol Multidose Dry Powder Inhaler (Albuterol MDPI) contains a formulation of albuterol sulfate (b) (4) and lactose monohydrate (b) (4) 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). Each inhaler device will be manufactured with (b) (4) labeled as 200 doses to help insure that patients do not inadvertently deplete their inhaler.

The Sponsor is proposing the use of 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Treatments for the Treatment of Bronchospasm

Inhaled corticosteroids		
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**
Combination Inhalers		
Generic Name	**Brand Name**	**Dosage**
Budesonide+Formoterol	**Symbicort**	**80/160 mcg + 4.5 mcg/inhalation**
Fluticosone+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 mg/inhalation**
Long-acting β-agonists		
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**
Leukotriene modifiers		
Generic Name	**Brand Name**	**Dosage**
Montelukast	**Singulair**	**4/5 mg tablets**
Zafirlukast	**Accolate**	**10/20 mg tablets**
Zileuton	**Zyflo CR**	**600 mg tablets**
Immunomodulators		
Generic Name	**Brand Name**	**Dosage**
Omalizumab	**Xolair**	**150 mg/vial**
Short-acting β-agonists		
Generic Name	**Brand Name**	**Dosage**
Albuterol Sulfate HFA	ProAir/Ventolin HFA	90 mcg/inhalation
Albuterol Sulfate	Generic for nebulization	0.083% and 0.5% solution
Ipatropium Bromide HFA	Atrovent HFA	17 mcg/inhlation
Ipatropium Bromide+Albuterol	Combivent/Respimat	20 mcg+100 mcg/inhalation
Levalbuterol HCl	Xopenex	45 mcg/inhalation
Tiotropium Bromide	Spiriva	18 mcg/capsule/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 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 β_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 bronchodialator. 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

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 ≥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 ≥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:

- (b) (4) 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
- (b) (4) was used in the supportive studies ABS-AS-101, ABS-AS-201, and ABS-AS-306
- (b) (4) was used in the pivotal safety studies in asthma: ABS-AS-301, -304 and -307.

The Sponsor discovered a problem with the (b) (4) Consequently, the Sponsor redesigned the device, (b) (4) which was used in the pivotal phase 3 studies. Additionally, the (b) (4) device reliability was evaluated in Study ABS-AS-308.

2.6 Other Relevant Background Information

For the purposes of this application, the Sponsor has requested a Pediatric Deferral for studies in children ages 4-11 years of age, and a Pediatric Waiver for studies in children younger than four years of age.

A pediatric clinical program studying Albuterol MDPI using the (b) (4) device is ongoing with two studies 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. StudyABS-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 is currently ongoing 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:

- (b) (4)
  - Studies ABS-AS-301, -302, -306, -307, and -308
  - Speaker and consulting fees of $156,700 (2010-2014)
- (b) (4)
  - Studies ABS-AS-301, -302, and -307
  - (b) (4) $199,500 (b) (4)
- (b) (4)
  - Studies ABS-AS-301, -302, -307, and -308
  - (b) (4) $63,250 (b) (4)
- (b) (4)
  - Study ABS-AS-304
  - (b) (4) $23,550 (b) (4)
- (b) (4)
  - Study ABS-AS-304
  - (b) (4) $351,454 (b) (4) $80,000 (b) (4)

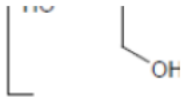
Overall, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study. In all cases, the applicant took steps to minimize potential bias which primarily consisted of excluding the investigator from the selection 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)) and lactose (b) (4) The new device will be marketed as a novel breath-actuated, dry powder inhaler with integrated dose counter that is (b) (4) 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). Each inhaler device will be manufactured (b) (4) labeled as 200 doses (b) (4)

The Chemistry, Manufacturing, and Controls (CMC) reviewer, Yong Hu, 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. Hu for a detailed analysis of the CMC aspects related to this application.

4.2 Clinical Microbiology

Not applicable.

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 Nikunj S Patel, PhD who recommends approval of Albuterol MDPI based on his analysis of the data submitted to the application. The reader is referred to the nonclinical review by Dr. Patel 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 β_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 Studies ABS-AS-101 and -201. 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 the 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-101	USA	47	A-MDPI PA-HFA	Phase 1, comparative, cumulative single-dose study in subjects with persistent asthma	Comparison of A-MDPI vs. PA-HFA after cumulative dose of 1440 mcg
ABS-AS-201	USA	72	A-MDPI PA-HFA	Phase 2, single-dose, dose-ranging study in subjects with persistent asthma	Assess efficacy and safety of 2 doses of A-MDPI vs. PA-HFA
ABS-AS-301	USA	158	A-MDPI PBO-MDPI	Phase 3, 12-wk, MC, R, DB, PC, repeat dose, parallel group study in subjects with persistent asthma	Assess efficacy and safety of A-MDPI vs. PBO-MDPI
ABS-AS-302	USA	38	A-MDPI PBO-MDPI	Phase 3, single-dose, R, DB, PC, 2-treatment, 2-sequence, 2-way crossover study in subjects with exercise-induced asthma	Assess efficacy and safety of A-MDPI vs. PBO-MDPI
ABS-AS-304	USA	160	A-MDPI PBO-MDPI	Phase 3, 12-wk, MC, R, DB, PC, repeat dose, parallel group study in subjects with persistent asthma	Assess efficacy and safety of A-MDPI vs. PBO. PK sub-study.
[redacted] (b) (4)					
ABS-AS-307	USA	337	A-MDPI	Phase3, DB, PC, 12-wk treatment with 40-wk OL, active treatment only study in subjects with persistent asthma	Assess safety of A-MDPI over 52-wks
ABS-AS-308	USA	345	A-MDPI	Phase 3, OL study over 36 or 50 days	Assess A-MDPI performance of device with dose counter with patients

A-MDPI: Albuterol MDPI; PA-HFA: ProAir HFA; PK: pharmacokinetics

5.2 Review Strategy

The clinical development program for Albuterol MDPI included eight studies that were all conducted in the US (Table 2). All studies were completed as planned except for

(b) (4)

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_1 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_1 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_1 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_1 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 or exercise-induced bronchospasm and met the required predicted FEV_1 values and bronchoconstriction reversibility criteria required for each study inclusion criteria. All exercise-induced asthma patients met the required minimum decrease in FEV_1 following an exercise challenge. 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. Subjects enrolled in the efficacy studies ranged in ages between 12 and 83 years of age, which is consistent with the proposed treatment indications.

Five of the studies were specifically designed to evaluate Albuterol MDPI for efficacy: Studies ABS-AS-101, -201, -301, and -304 evaluated the product in patients with persistent asthma and Study ABS-AS-302 evaluated the product in patients with exercise-induced asthma. Data from Studies ABS-AS-301, -304, and -307 comprised the primary focus for the safety evaluation given the overall study design, large subject cohorts, and placebo-controlled periods. Data from Studies ABS-AS-307 and -308 were used to assess the Albuterol MDPI device counter's reliability. Although Studies ABS-AS-101 and -201 were technically pharmacokinetic/pharmacodynamic studies, their results will be discussed in the Review of Efficacy section (Section 6) as their results directly pertain to the clinical activity of the active moiety, albuterol sulfate. Similarly, the results of Studies ABS-AS-307 and -308, which did not directly assess efficacy, will also be discussed in the Review of Efficacy section (Section 6) because the assessment of the function and reliability of the new MDPI device with integrated counter is particularly important for the current application.

Study ABS-AS-101 (Section 5.3.1.1) was a phase 1 study that compared five cumulative doses of Albuterol MDPI 90 mcg and ProAir HFA 90 mcg administered as 1+1+2+4+8 inhalations for a total albuterol dose of 1440 mcg. Results from this study were used to demonstrate the efficacy of Albuterol MDPI compared to ProAir HFA over a range of doses. The primary endpoint was the baseline-adjusted FEV_1 30-minutes after each of the five cumulative doses. Additionally, the pharmacodynamics effects (e.g., plasma glucose concentrations, heart rate) of the two treatments were also analyzed. Although the statistical analysis plan intended to determine non-inferiority between the products, the Sponsor's proposed non-inferiority margin was calculated incorrectly, therefore the results from the study were considered descriptive rather than

confirmatory based on means and 90% CI for differences in efficacy between Albuterol MDPI and ProAir HFA. Overall the study was well conducted and suggested that the two albuterol products were similar at a clinical level.

Study ABS-AS-201 (Section 5.3.1.2) was a phase 2 dose-ranging study that evaluated the efficacy of Albuterol MDPI 90 mcg, Albuterol 180 mcg, ProAir HFA 90 mcg, ProAir HFA 180 mcg, compared to placebo. These data confirmed the efficacy of albuterol, as both Albuterol MDPI and ProAir HFA, in subjects with asthma compared to placebo. A dose-response within treatment arms could be generally appreciated, although not statistically significant. Similar to Study ABS-AS-101, the results from the study demonstrated the efficacy of both albuterol products and also suggest that the two products performed similarly at a clinical level.

Studies ABS-AS-301 and -304 (Section 5.3.1.3 and 5.3.1.5) were similarly designed and well conducted large phase 3 studies used to support the efficacy and safety of Albuterol MDPI at the proposed recommended dosing in patients with persistent asthma, one of the two proposed clinical indications for this application. Given their similarity, the two studies are reviewed together in Section 6.1.4.3, and in conjunction with Study ABS-AS-307, comprise the majority of the safety database. These studies demonstrated a clinically meaningful benefit and acceptable safety profile of Albuterol MDPI to patients with persistent asthma at the recommended dosing.

Study ABS-AS-302 (Section 5.3.1.4) was a phase 3 study designed to assess the efficacy and safety of Albuterol MDPI in subjects with exercise-induced asthma, the second of the two proposed clinical indications for this application. The study was well conducted and demonstrated a clear advantage of Albuterol MDPI in preventing the bronchospasm associated with exercise-induced asthma.

Studies ABS-AS-307 and -308 (Sections 5.3.1.6 and 5.3.1.7) were designed to assess the functionality and reliability of the Albuterol MDPI with dose counter device. The results from this study are demonstrated the proposed new Albuterol MDPI device to be reliable and the dose counter to be accurate with very low incidences of undercounting.

Safety data from Studies ABS-AS-301, -304, and -307 provide the pivotal safety information for Albuterol MDPI. All three studies were designed to include a 12-week double-blind treatment period utilizing the MDPI device proposed for marketing. These studies allow for the direct comparison between treatment and placebo allowing for a more complete evaluation of potential safety signals with Albuterol MDPI.

Supportive safety data are provided from Studies ABS-AS-101, -201, -302, and -308, which will be discussed separately from the pooled analyses in the relevant safety sections. Additionally, safety data from Albuterol MDPI-related studies involving the failed device (Study ABS-AS-306) and salbumatol will be discussed.

(b) (4)

Studies IX-100-076 and IX-101-076 were conducted with salbutamol (albuterol) MDPI that utilized a higher dose (100 mcg of albuterol base). Study IX-100-076 was a

randomized, single blind, placebo/active-controlled, five-treatment, cumulative dose (maximum eight inhalations), five-period crossover study and Study IX-101-076 was an open-label study of three increasing single doses of salbutamol-MDPI with no comparator.

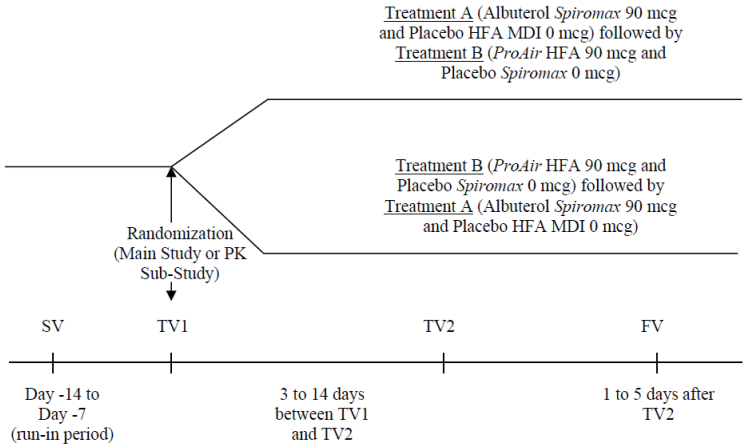
5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Studies Included in the Assessment of Efficacy

5.3.1.1 ABS-AS-101

Study ABS-AS-101, entitled "*Cumulative Dose Comparison of the Efficacy and Safety of Albuterol Spiromax and ProAir HFA in Adult Patients with Asthma"*, was conducted between February 13, 2010 and June 21, 2010 and was designed as a phase 1, multicenter (eight sites throughout the US), randomized, double-blind, double-dummy, cumulative-dose, crossover study in adult subjects (18 to 45 years of age) with persistent asthma. The primary objective of the study was to compare the efficacy of inhaled albuterol MDPI and inhaled ProAir HFA after a cumulative dose of 1440 mcg administered as 1+1+2+4+8 inhalations of 90 mcg per inhalation. After an initial screening visit, subjects entered a Run-in Period of 7 to 14 days prior to their first of two treatment visits that were separated by 3 to 14 days of washout. A final follow-up visit was performed 1 to 5 days after subjects' last treatment visit. Figure 2 shows an overview of Study ABS-AS-101:

Figure 2. Study Design



*source: Clinical Study Report-Protocol # ABS-AS-101, page 33

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 18 to 45 years
    - Diagnosis of asthma in accordance with NAEPP guidelines
    - Asthma (FEV_1 50 to 80% predicted for age, height, gender, and race) of a minimum of 6 months duration that was stable for at least 30 days prior to the screening visit
    - Use of inhaled corticosteroids for persistent asthma at a stable, low to medium dose for ≥4 weeks
    - Able to perform acceptable and reproducible spirometry according to protocol guidelines
    - Demonstration of reversible bronchoconstriction consisting of ≥15% increase from baseline FEV_1 within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA
    - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study
    - Resting heart rate of ≥50 to ≤90 beats per minute (bpm) and blood pressure of ≤140/90 mmHg
- 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
- Women who were pregnant or nursing
- History or current of respiratory infection or disorder within 14 days preceding the screening visit
- History or current evidence of any concurrent medical disorder
- History of malignancy in the past 5 years
- Clinically significant ECG or laboratory abnormalities
- Use of any protocol-prohibited medications

Subjects were permitted to receive the following medications during the washout periods but were withheld as pre-specified prior to the screening visit and throughout each of the two Treatment Visit days:

- Short-acting β_2-adrenergic agonists
- Orally inhaled anti-cholinergics
- Alcohol
- Foods and beverages containing methyl xanthines or compounds known to inhibit CYP3A4 (e.g., grapefruit)

Subjects were to be on stable doses (≥4 weeks) of inhaled corticosteroids of a low to medium dose defined as the equivalent of ≤500 mcg/day of fluticasone proprionate throughout the study. Prohibited concomitant medications included, but were not limited to, systemic corticosteroids, omalizumab, β_2-adrenergic antagonists, long-acting β_2-adrenergic agonists, cromolyns, leukotriene modifiers, long-acting antihistamines, tricyclic antidepressants, and MAO inhibitors.

During each treatment visit, an individual subject was given one of the following treatments in a randomized sequence in a two-period crossover manner:

- Albuterol MDPI 90 mcg and placebo HFA MDI
- ProAir HFA 90 mcg and placebo Albuterol MDPI

At each treatment visit, the assigned treatment was administered by cumulative dosing of 1+1+2+4+8 inhalations from each device with each inhalation separated by three minute intervals. Placebo was administered with the alternate device.

The primary efficacy endpoint of the study was the baseline-adjusted FEV_1 at 30 minutes after each of the five cumulative doses. Major secondary pharmacodynamic endpoints included change from baseline in plasma potassium 15 minutes after each cumulative dose; change from baseline in heart rate 15 minutes after each cumulative dose; change from baseline in plasma glucose 15 minutes after each cumulative dose; and changes in QTc as determined from serial ECGs. The primary statistical analysis was the mixed-effect ANOVA with fixed effects of baseline FEV_1, sequence, treatment (device) group, period, site, cumulative dose, treatment x cumulative dose, and random effect for subject within sequence. The primary analysis was based upon a comparison of Albuterol MDPI and ProAir HFA with respect to the change from baseline in the last FEV_1 obtained at 30 minutes post-dose after each of the cumulative doses: 90 mcg, 180 mcg, 360 mcg, 720 mcg, and 1440 mcg, for the Per-Protocol Primary Population. Albuterol MDPI and ProAir HFA were declared equivalent if, at each cumulative dose, the null hypothesis that the difference in mean change from baseline in FEV_1 between the treatments was greater than 0.20 L was rejected. This hypothesis was tested at the 0.05 level of significance by testing at each cumulative dose the null hypotheses that the absolute difference in means was greater than 0.20 L at the 0.05 level of significance. Albuterol MDPI and ProAir HFA were declared equivalent if the 90% CI for the difference in treatment means for the change from baseline in FEV_1 30 minutes post-dose after each cumulative dose were all within the limits ± 0.20 L. A full discussion of the statistical analyses can be found in Dr. Abugov'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 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 events 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 47 subjects with persistent asthma were randomized to the study, with 24 of the subjects also being randomized to participate in the PK substudy as planned in the study protocol. Two randomized subjects (4%), one from each treatment arm, discontinued the study due to withdrawal of consent.

All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded; however, analysis populations were initially pre-defined but subsequently re-defined after analysis of the unblinded data from Site 3733 demonstrated that four subjects had an insufficient number of samples and/or high pre-dose plasma albuterol levels. All data from Site 3733 was excluded from analyses for efficacy, PK and pharmacodynamics. Consequently, the re-defined “Per-Protocol Initial Population” was used for the primary analyses. Exclusion of subjects from Site 3733 is not expected to affect the interpretation of the results for the study.

There was one major protocol deviation reported involving Subject 3733/1011 who had a dose of study drug outside of the pre-defined treatment window due to a “sneezing fit” and restroom use. As a result, the time of administration for Dose 5 increased from the per protocol window of 7.5 minutes to 25 minutes. As discussed above, data from this patient was excluded from the per-protocol analyses.

Overall, the baseline demographics and disease characteristics were similar between treatment arms with the average patient being approximately 33 years of age, White, and with equal proportions of males and females (51% vs. 49%, respectively). All subjects had been diagnosed with asthma.

5.3.1.2 ABS-AS-201

Study ABS-AS-201, entitled “A Double-Blind, Randomized, Placebo-Controlled, 5-Way Crossover, Multicenter, Single Dose, Dose-Ranging Study to Compare the Efficacy and Safety of Albuterol Spiromax and ProAir HFA in Adult and Adolescent Subjects Ages 12 and Older with Persistent Asthma”, was conducted between February 22, 2010 and June 01, 2010. The study was designed as a multicenter, randomized, double-blind, double-dummy, single-dose, five-treatment, 10-sequence, placebo-controlled, crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in male and female subjects age 12 and older with persistent asthma. The primary objective of the study was to assess the efficacy of two doses of albuterol delivered as either Albuterol MDPI or ProAir HFA compared to placebo.

The study consisted of three periods with seven subject visits. Following an initial screening visit, subjects entered a 14-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 14-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 at ~8:00 AM 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 (Table 3).

Table 3. Study Medication

Treatment	Dosage
Placebo	0 mcg single dose
Albuterol MDPI	90 mcg single dose
Albuterol MDPI	180 mcg single dose
ProAir HFA	90 mcg single dose
ProAir HFA	180 mcg single dose

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 12 years or older
    - Diagnosis of asthma in accordance with NAEPP guidelines
    - Asthma (FEV1 50 to 80% predicted for age, height, gender, and race) of a minimum of 6 months duration that was stable for at least 30 days prior to the screening visit
    - Persistent asthma for ≥6 months duration that had been stable for ≥4 weeks prior to the screening visit.
    - Use of inhaled corticosteroids for persistent asthma at a stable, low to medium dose for ≥4 weeks
    - Able to perform acceptable and reproducible PEF measurements

  - Demonstration of reversible bronchoconstriction consisting of ≥15% increase from baseline FEV1 within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA
  - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

- 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
  - Women who were pregnant or nursing
  - History or current of respiratory infection or disorder within 14 days preceding the screening visit
  - History or current evidence of any concurrent medical disorder
  - History of malignancy in the past 5 years
  - Clinically significant ECG or laboratory abnormalities
  - Use of any protocol-prohibited medications

Subjects were permitted to receive the following medications during the washout periods but were withheld as pre-specified prior to the screening visit and throughout the treatment/PK days:

- Short-acting β2-adrenergic agonists
- Orally inhaled anti-cholinergics
- Alcohol
- Foods and beverages containing methyl xanthines or compounds known to inhibit CYP3A4 (e.g., grapefruit)

Subjects were to be on stable doses (≥4 weeks) of inhaled corticosteroids of a low to medium dose defined as the equivalent of ≤500 mcg/day of fluticasone proprionate throughout the study. Prohibited concomitant medications included, but were not limited to, systemic corticosteroids, omalizumab, β_2-adrenergic antagonists, long-acting β2-adrenergic agonists, cromolyns, leukotriene modifiers, long-acting antihistamines, tricyclic antidepressants, and MAO inhibitors.

The primary efficacy endpoint of the study was the baseline-adjusted area under the effect curve (AUEC) for FEV_1 observed up to 6 hours following completion of dosing (FEV_1 AUEC0-6) measured in L*hr. The primary statistical analysis was the mixed-effect ANOVA with fixed effects of baseline FEV_1, 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 Dr. Abugov'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 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 72 subjects were randomized at 12 study sites throughout the US. Subject 371901 was incorrectly entered into the IVRS system as "randomized" and subsequently withdrawn from the study prior to receiving study treatment. Of the remaining 71 subjects who received ≥1 dose of study drug, 68 completed the study. Three subjects discontinued the study: one subject was lost to follow-up, one subject was withdrawn due to a treatment visit date outside the protocol window, and one subject withdrew consent.

The Intent-to-Treat population included all randomized subjects who received ≥1 dose of randomized study drug and had ≥1post-baseline assessment. This population was used for the primary efficacy analysis. The Safety population included all randomized subjects who received ≥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.

There was one major protocol deviation reported involving Subject 372011 who after completing the study was found to have enrolled at two other study sites while participating in Study ABS-AS-201. Consequently, data for this subject were excluded from the Per-Protocol population. The remaining protocol violations were deemed minor and were related to protocol compliance issues. 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 43 years of age (range 12-

83 years), white (76%), and with a greater proportion of females than males (58% vs. 42%, respectively). Only three patients between the ages of 12 to 18 years of age were randomized in the study. All subjects had persistent asthma for ≥6 months that had been medically stable for ≥4 weeks prior to screening.

5.3.1.3 ABS-AS-301

Study ABS-AS-301, entitled "*A 12-Week Comparison of the Efficacy and Safety of Albuterol MDPI versus Placebo in Subjects 12 Years and Older with Persistent Asthma*", was conducted between December 3, 2012 and November 5, 2013. The study was designed as a phase 3, 12-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 male and female subjects age 12 years and older 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 12-week period in subjects diagnosed with persistent asthma and on a stable dose of inhaled corticosteroids.

The study consisted of three periods: a Screening/Run-in Period of 14 days; Treatment Period of 12 weeks; and a Follow-up Period of 7 days. Following an initial screening visit, subjects entered a 14-day Run-in Period prior to their first treatment visit during which time they self-administered single-blinded Placebo MDPI QID. All subjects were provided with an albuterol HFA MDI to use as needed for the treatment of any breakthrough asthma symptoms. During the Run-in Period and throughout the remainder of the study, subjects recorded information in a daily diary regarding study drug use, assessment of daily asthma symptom scores, number of rescue medication inhalations used, peak expiratory flow rate measured each morning after assessment of asthma symptoms, and information regarding adverse events, subject's general health, and any issues with the inhaler device.

Subjects who qualified to enter the Treatment Period of the study were randomized into one of two treatment arms as follows:

- Albuterol MDPI 90 mcg/inhalation, 2 inhalations QID (~ 7 AM, 12 PM, 5 PM, Bedtime)
- Placebo MDPI 0 mcg/inhalation, 2 inhalations QID (~ 7 AM, 12 PM, 5 PM, Bedtime)

Subjects continued with their assigned study drug during the 12-week, double-blind, dosing period. All subjects were provided with a rescue albuterol HFA MDI inhaler to use as needed for relief of asthma symptoms. During the Treatment Period, subjects had study site visits at Days 8, 22, and then every 21 days with phone contact with investigators between study site visits.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 12 years or older
    - Diagnosis of asthma in accordance with NAEPP guidelines
    - Asthma (FEV1 50 to 80% predicted for age, height, gender, and race) of a minimum of 6 months duration that was stable for at least 30 days prior to the screening visit
    - Persistent asthma for ≥6 months duration that had been stable for ≥4 weeks prior to the screening visit.
    - Use of inhaled corticosteroids for persistent asthma at a stable, low to medium dose for ≥4 weeks (defined as the equivalent of ≤500 mcg/day of fluticasone proprionate)
    - Able to perform acceptable and reproducible PEF measurements
    - Demonstration of reversible bronchoconstriction consisting of ≥15% increase from baseline FEV1 within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA
    - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study
- 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

- Women who were pregnant or nursing
- History or current of respiratory infection or disorder within 14 days preceding the screening visit
- History or current evidence of any concurrent medical disorder
- History of malignancy in the past 5 years
- Clinically significant ECG or laboratory abnormalities
- Use of any protocol-prohibited medications

Subjects meeting the following criteria at the first Treatment Visit were randomized:

- Subject continued to have a FEV1 within 50 to 80% of predicted normal for adults or 50 to 85% for adolescents
- Subject did not experience an adverse event that would preclude them meeting selection criteria
- Subject adequately completed the daily diary and complied with the scheduled study drug administration
- Subject had not used any protocol-prohibited medications during the Run-in Period

Subjects who withdrew, were withdrawn, or were lost to follow-up from the Run-in Period were not replaced. Subjects meeting all inclusion/exclusion and randomization criteria were randomized in a 1:1 ratio receive double-blinded Albuterol MDPI or Placebo MDPI for 12-weeks. The following medications were allowed during the study but were withheld as pre-specified in the protocol prior to and during study site visits requiring spirometry assessments:

- Short-acting β2-adrenergic agonists
- Stable doses of inhaled corticosteroids
- Antihistamines
- Decongestants
- Alcohol
- Foods and beverages containing methyl xanthines or compounds known to inhibit CYP3A4 (e.g., grapefruit)

Subjects were to be on stable doses (≥4 weeks) of inhaled corticosteroids of a low to medium dose defined as the equivalent of ≤500 mcg/day of fluticasone proprionate throughout the study. Subjects taking long-acting β2-adrenergic agonists were discontinued from their medication if deemed safe by the principle investigator. Immunotherapy was permitted provided the subject was on a stable dose for ≥90 days prior to study entry. The use of non-glucocorticoid-containing nasal sprays (e.g., Nasalcrom) was prohibited during the course of the study. Prohibited concomitant medications included, but were not limited to, systemic corticosteroids, omalizumab, β2-adrenergic antagonists, long-acting β2-adrenergic agonists, cromolyns, leukotriene modifiers, long-acting antihistamines, tricyclic antidepressants, and MAO inhibitors.

The primary efficacy endpoint of the study was the baseline-adjusted area under the effect curve (AUEC) for FEV_1 observed up to 6 hours following completion of dosing (FEV_1 AUEC0-6) measured in L*hr over the 12-week treatment period. The primary statistical analysis was the mixed-model repeated-measures analysis with baseline-adjusted FEV_1 $AUEC_{0-6}$ over the 12-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. Abugov'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 were three amendments made to the protocol that largely detailed clarifications to protocol procedures. Additionally, the Sponsor had notified the Division of a change in the analyses due to an inadvertent omission from the statistical analysis plan that stated a logistic regression analysis would be used to model the percent of 12% and 15% responders. 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 172 subjects were initially enrolled and entered into the Run-in Period of the study; however, 14 of these subjects were not randomized due to failing randomization criteria. Consequently, 158 subjects were randomized at 26 study sites throughout the US to receive study drug with 79 subjects randomized to Placebo MDPI and 79 Subjects to Albuterol MDPI. One subject randomized to the Albuterol MDPI treatment arm was not treated resulting in only 78 subjects being treated with Albuterol MDPI. The Intent-to-Treat population and the Full Analysis Set consisted of 157 subjects. Six (4%) subjects discontinued the study: one subject from the Albuterol MDPI arm and five

subjects from the Placebo MDPI arm. Withdrawal of Consent was the most common reason for discontinuation from the study.

There were nine (6%) subjects with ≥1 protocol violations:

- Placebo MDPI treatment arm (n=6)
    - excluded concomitant medication (n=4)
    - failure to meet inclusion criteria (n=2)
- Albuterol MDPI treatment arm (n=3)
    - failure to meet inclusion criteria (n=3)

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 39 years of age (range 12-70 years), white (72%), and with a greater proportion of females than males (58% vs. 42%, respectively). Approximately equal proportions of children aged 12 to 17 years were enrolled in the Placebo MDPI and Albuterol MDPI treatment arms, 14 (18%) and 16 (20%), respectively. All subjects carried a diagnosis of persistent asthma and baselin FEV_1 were comparable between treatment arms.

5.3.1.4 ABS-AS-302

Study ABS-AS-302, entitled "*A Single-Dose Study to Assess the Efficacy of Albuterol Spiromax in Adult and Adolescent Patients with Exercise-Induced Bronchoconstriction (EIB)*", was conducted between March 26, 2013 and June 4, 2013. The study was designed as a phase 3, single-dose, randomized, double-blind, placebo-controlled, two-treatment, two-sequence, two-way crossover, multicenter study of Albuterol MDPI compared to Placebo MDPI in male and female subjects age 12 to 50 years of age with

a documented history of exercise-induced asthma. The primary objective of the study was to assess the efficacy of a single-dose (two inhalations) of Albuterol MDPI 90 mcg/inhalation compared to Placebo MDPI in subjects experiencing exercise-induced bronchoconstriction.

The study consisted of two screening visits and two treatment visits with each requiring an exercise challenge. A final follow-up visit was conducted via a telephone encounter. The initial screening visit entailed general screening procedures, spirometry, demonstration of exercise-induced bronchoconstriction, and establishment of treadmill criteria. All spirometry and testing procedures were in accordance with current guidelines. To be eligible for the treatment period of the study, subjects were required to meet the following criteria at the Screening Visit-1:

- Pre-exercise challenge best FEV1 (performed at 30 minutes and 5 minutes prior to exercise challenge) was ≥70% of predicted value
- Exercise-induced bronchoconstriction as demonstrated by a ≥20% decrease from the five-minute pre-exercise challenge absolute FEV1

If any of the spirometry criteria were not met at the first screening visit, subjects were then retested within seven days of the initial visit. Only one retest was permitted for any reason prior to randomization and those subjects not meeting criteria were considered a screening failure.

At Screening Visit-2, subjects again underwent general screening procedures, spirometry, and demonstration of exercise-induced bronchoconstriction. The first spirometry assessment was performed at approximately the same time as the subject's initial assessment at Screening Visit-1. Subjects were administered Placebo MDPI and were required to meet the following criteria:

- The pre-dose Placebo MDPI, pre-exercise challenge best FEV1 (performed at 30 minutes and 5 minutes prior to exercise challenge) was ≥70% of predicted value

- The post-dose Placebo MDPI, pre-exercise challenge best FEV1 (performed 30 minutes post-dose) was ≥70% of predicted value
- The best pre-dose, pre-challenge FEV1 value measured was not greater than ±15% of the best pre-challenge FEV1 value measured at the first screening visit
- Exercise-induced bronchoconstriction as demonstrated by a ≥20% decrease from the post-dose pre-exercise challenge absolute FEV1
- No development of a respiratory tract infection or asthma exacerbation between screening visits

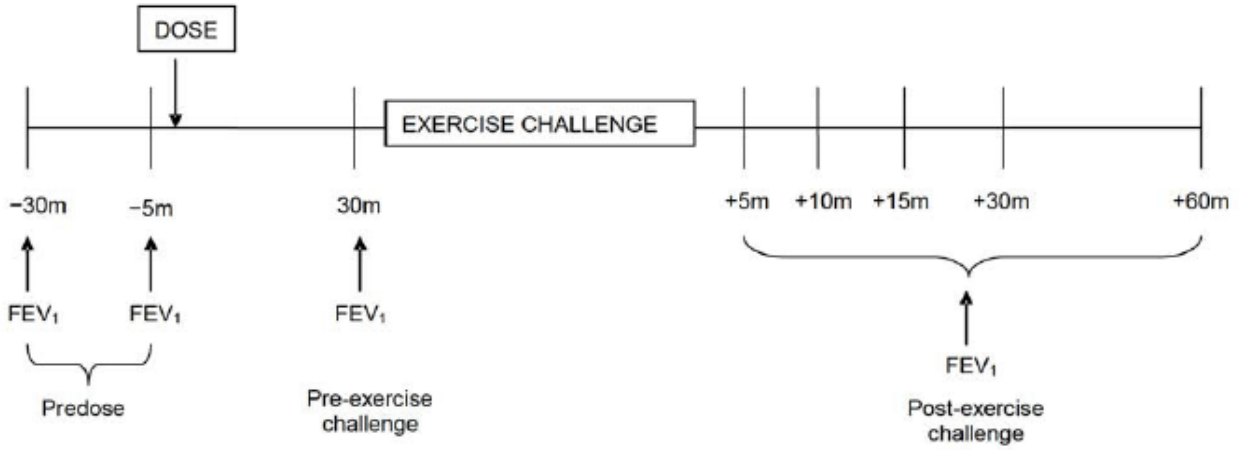
If any of the spirometry criteria were not met at the second screening visit, subjects were then retested within seven days of the initial visit. Only one retest was permitted for any reason prior to randomization and those subjects not meeting criteria were considered a randomization failure.

Treatment visits entailed general testing procedures, spirometry, and demonstration of exercise-induced bronchoconstriction. Single doses of Albuterol MDPI 180 mcg or Placebo MDPI were administered. Subjects had to meet the following spirometry criteria to continue in the study:

- The pre-dose, pre-exercise challenge best FEV1 measurements (performed at 30 minutes and 5 minutes prior to exercise challenge) were ≥70% of predicted value
- The post-dose, pre-exercise challenge FEV1 determination (performed 30 minutes post-dose, immediately prior to exercise challenge) was ≥70% of predicted value
- The best pre-dose, pre-challenge FEV1 values measured at both treatment visits did on exceed ±15% of the best pre-challenge FEV1 value measured at the initial screening visit

Figure 3 illustrates the spirometry measurements at Screening Visit-2 and both treatment visits.

Figure 3. Spirometry Measurements



source: Sponsor Clinical Study Report ABS-AS-302, Figure 1

Similar to the screening visits, if any of the spirometry criteria were not met, subjects could be retested within seven days of the treatment visit. Only one retest was permitted for any reason prior to randomization. Subjects who developed a respiratory tract infection or asthma exacerbation between Screening Visit-2 and Treatment Visit-1 could be re-screened between tow and four weeks following resolution of symptoms. In the event that the subject experienced an asthma exacerbation, all screening procedures were repeated; however, repeat screening was not permitted for subjects who were treated with oral corticosteroids or required hospitalization.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 12 to 50 years or old
    - Documented history of exercise-induced asthma, with or without underlying asthma
    - Exercise-induced asthma as defined by a ≥20% decrease from the five-minute pre-exercise challenge FEV1 observed within 60 minutes following an exercise challenge at Screening Visit-1
    - Each pre-exercise challenge best FEV1 determination was ≥70% predicted for age, height, gender, and race

  - Use of inhaled corticosteroids was permitted for subjects with underlying asthma provided a stable, low to medium dose for ≥4 weeks (defined as the equivalent of ≤500 mcg/day of fluticasone proprionate)
  - Able to perform acceptable and reproducible spirometry measurements

- 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
  - Women who were pregnant or nursing
  - History or current of respiratory infection or disorder within 14 days preceding the screening visit
  - History or current evidence of any concurrent medical disorder
  - History of malignancy in the past 5 years
  - Clinically significant ECG or laboratory abnormalities
  - Use of any protocol-prohibited medications

Subjects meeting the criteria as outlined above were randomized in a 1:1 ratio to one of two treatments in a two-way, crossover design:

- Albuterol MDPI 90 mcg/inhalation, 2 inhalations (as a single dose)
- Placebo MDPI 0 mcg/inhalation, 2 inhalations (as a single dose)

The following medications were allowed with restrictions

- Inhaled short-acting β2-adrenergic agonists were to be discontinued ≥8 hours prior to spirometry
- Oral short-acting β2-adrenergic agonists were to be discontinued ≥72 hours prior to spirometry
- Albuterol MDI was permitted as rescue medication during the exercise challenge and afterwards as needed during testing
- Stable doses of low to moderate potency inhaled corticosteroids (defined as the equivalent of ≤500 mcg/day of fluticasone proprionate)
- Antihistamines were to be discontinued ≥24 hours prior to spirometry
- Xanthine derivatives were to be discontinued ≥72 hours prior to spiromety

- Cromolyn, nedocromil, or lodoxamide were to be discontinued ≥8 hours prior to spirometry
- Stable maintenance doses of immunotherapy for the treatment of allergy ≥90 days was permitted

Additional prohibited medications included, but were not limited to, systemic corticosteroids, omalizumab, β2-adrenergic antagonists, long-acting β2-adrenergic agonists, cromolyns, leukotriene modifiers, long-acting antihistamines, tricyclic antidepressants, and MAO inhibitors.

The primary efficacy endpoint of the study was the maximum percentage fall from baseline in FEV_1 observed up to 60 minutes post-exercise challenge. The primary statistical analysis was the mixed-effect ANOVA with fixed effects of sequence, treatment group, period, and center, within period baseline FEV_1 as a covariate, and random effect for patient within sequence. An appropriate contrast was derived from this model for the mean difference in the primary efficacy variable: the maximum percentage fall from baseline in FEV_1 observed up to 60 minutes post-exercise challenge. Efficacy was declared if this difference was negative and significant at the 0.05 level.

There were no formal amendments made to the protocol; however, a change to the planned statistical analysis plan was made. Due to the planned mixed logistic model failed to converge, a logistic model using a GEE algorithm was used instead to analyze the proportion of “protected” patients. This model was used in place of the linear mixed model described in the statistical analysis plan to be used if there were convergence problems, as it was deemed the most appropriate alternative model to use. An additional sensitivity analysis using a nonparametric analysis for a binary crossover variable also was used to compare the proportion of “protected” patients. A full discussion of the statistical analyses can be found in Dr. Abugov’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 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 38 subjects were randomized at five study sites throughout the US with 19 subjects randomized to Placebo/Albuterol MDPI sequence and 19 subjects to the Albuterol/Placebo MDPI sequence. All subjects completed the study, although one subject from each treatment arm was not included in the Per-Protocol Population.

There were two (2%) subjects with ≥1 protocol violations related to inclusion criteria involving one subject from each treatment arm. The overall number and type of protocol violations were similar across study arms and are not expected to affect the interpretation of the results.

In general, the baseline demographics and disease characteristics were similar between treatment arms with the average patient being approximately 32 years of age (range 16-

50 years), white (79%), and approximately equal proportions of females and males (50% vs. 50%, respectively). Two 16-year-old subjects were enrolled and were randomized to one in each treatment arm.

5.3.1.5 ABS-AS-304

Study ABS-AS-304, entitled "*A 12-Week Comparison of the Efficacy and Safety and Steady-State Pharmacokinetics of Albuterol MDPI versus Placebo in Subjects 12 Years and Older with Persistent Asthma*", was conducted between December 3, 2012 and November 2, 2013. The study was designed as a phase 3, 12-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 male and female subjects age 12 and older 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 12-week period in subjects diagnosed with persistent asthma and on a stable dose of inhaled corticosteroids.

The study consisted of three periods: a Screening/Run-in Period of 14 days; Treatment Period of 12 weeks; and a Follow-up Period of 7 days. Following an initial screening visit, subjects entered a 14-day Run-in Period prior to their first treatment visit during which time they self-administered single-blinded Placebo MDPI QID. All subjects were provided with an albuterol HFA MDI to use as needed for the treatment of any breakthrough asthma symptoms. During the Run-in Period and throughout the remainder of the study, subjects recorded information in a daily diary regarding study drug use, assessment of daily asthma symptom scores, number of rescue medication inhalations used, peak expiratory flow rate (PEFR) measured each morning after assessment of asthma symptoms, and information regarding adverse events, subject's general health, and any issues with the inhaler device.

Subjects who qualified to enter the Treatment Period of the study were randomized into one of two treatment arms as follows:

- Albuterol MDPI 90 mcg/inhalation, 2 inhalations QID (~ 7 AM, 12 PM, 5 PM, Bedtime)
- Placebo MDPI 0 mcg/inhalation, 2 inhalations QID (~ 7 AM, 12 PM, 5 PM, Bedtime)

Subjects continued with their assigned study drug during the 12-week, double-blind, dosing period. All subjects were provided with a rescue albuterol HFA MDI inhaler to use as needed for relief of asthma symptoms. During the Treatment Period, subjects had study site visits at Days 8, 22, and then every 21 days with phone contact with investigators between study site visits.

A subset of subjects were randomized to participate in a pharmacokinetics portion of the study which consisted of serial blood sampling over 10 hours at Treatment Visit-1 and over six hours at Treatment Visit-2.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 12 years or older
    - Diagnosis of asthma in accordance with NAEPP guidelines
    - Asthma (FEV1 50 to 80% predicted for age, height, gender, and race) of a minimum of 6 months duration that was stable for at least 30 days prior to the screening visit
    - Persistent asthma for ≥6 months duration that had been stable for ≥4 weeks prior to the screening visit.
    - Use of inhaled corticosteroids for persistent asthma at a stable, low to medium dose for ≥4 weeks (defined as the equivalent of ≤500 mcg/day of fluticasone proprionate)
    - Able to perform acceptable and reproducible PEF measurements
    - Demonstration of reversible bronchoconstriction consisting of ≥15% increase from baseline FEV1 within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA
    - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

- 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
    - Women who were pregnant or nursing
    - History or current of respiratory infection or disorder within 14 days preceding the screening visit
    - History or current evidence of any concurrent medical disorder
    - History of malignancy in the past 5 years
    - Clinically significant ECG or laboratory abnormalities
    - Use of any protocol-prohibited medications

Subjects meeting the following criteria at the first Treatment Visit were randomized:

- Subject continued to have a FEV_1 within 50 to 80% of predicted normal for adults or 50 to 85% for adolescents
- Subject did not experience an adverse event that would preclude them meeting selection criteria
- Subject adequately completed the daily diary and complied with the scheduled study drug administration
- Subject had not used any protocol-prohibited medications during the Run-in Period
- Appropriate washout of medications occurred to complete pharmacokinetics and spirometry

Subjects who withdrew, were withdrawn, or were lost to follow-up from the Run-in Period were not replaced. Subjects meeting all inclusion/exclusion and randomization criteria were randomized in a 1:1 ratio receive double-blinded Albuterol MDPI or Placebo MDPI for 12-weeks.

The following medications were allowed during the non-pharmacokinetic portion of the study but were withheld as pre-specified in the protocol prior to and during study site visits requiring spirometry assessments:

- Short-acting β2-adrenergic agonists
- Stable doses of inhaled corticosteroids
- Antihistamines
- Decongestants
- Alcohol
- Foods and beverages containing methyl xanthines or compounds known to inhibit CYP3A4 (e.g., grapefruit)

Subjects randomized to the pharmacokinetic substudy were also restricted from using inhaled anti-cholinergics ≥8 hours prior to Treatment Visits one and two.

Subjects were to be on stable doses (≥4 weeks) of inhaled corticosteroids of a low to medium dose defined as the equivalent of ≤500 mcg/day of fluticasone proprionate throughout the study. Subjects taking long-acting β2-adrenergic agonists were discontinued from their medication if deemed safe by the principle investigator. Immunotherapy was permitted provided the subject was on a stable dose for ≥90 days prior to study entry. The use of non-glucocorticoid-containing nasal sprays (e.g., Nasalcrom) was prohibited during the course of the study. Prohibited concomitant medications included, but were not limited to, systemic corticosteroids, omalizumab, β2-adrenergic antagonists, long-acting β2-adrenergic agonists, cromolyns, leukotriene modifiers, long-acting antihistamines, tricyclic antidepressants, and MAO inhibitors.

The primary efficacy endpoint of the study was the baseline-adjusted area under the effect curve (AUEC) for FEV_1 observed up to 6 hours following completion of dosing (FEV_1 AUEC0-6) measured in L*hr over the 12-week treatment period. The primary statistical analysis was the mixed-model repeated-measures analysis with baseline-adjusted FEV_1 AUEC0-6 over the 12-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. Abugov'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. 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 AEs 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 were three amendments made to the protocol that largely detailed clarifications to protocol procedures. Additionally, the Sponsor had notified the Division of a change in

the analyses due to an inadvertent omission from the statistical analysis plan that stated a logistic regression analysis would be used to model the percent of 12% and 15% responders. 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 175 subjects were initially enrolled and entered into the Run-in Period of the study; however, 15 of these subjects were not randomized due to failing randomization criteria. Consequently, 160 subjects were randomized at 29 study sites throughout the US to receive study drug with 85 subjects randomized to Placebo MDPI and 75 Subjects to Albuterol MDPI. One subject randomized to the Albuterol MDPI treatment arm was not treated resulting in only 78 subjects being treated with Albuterol MDPI. The Intent-to-Treat population consisted of 160 subjects and the Full Analysis Set consisted of 159 subjects. Thirteen (8%) subjects discontinued the study: six subjects from the Albuterol MDPI arm and seven subjects from the Placebo MDPI arm. Withdrawal of Consent was the most common reason for discontinuation from the study.

There were two (1%) subjects with ≥1 protocol violations related to inclusion criteria involving one subject from each treatment arm. 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 38 years of age (range 12-74 years), white (78%), and approximately equal proportions of females and males (51% vs. 49%, respectively). Approximately equal proportions of children aged 12 to 17 years were enrolled in the Placebo MDPI and Albuterol MDPI treatment arms, 17 (20%) and 14 (19%), respectively.

5.3.5.6 Study ABS-AS-307

Study ABS-AS-307, entitled "*A Multi-Center 52-Week Study to Assess the Safety of Albuterol MDPI in Subjects with Asthma*", was conducted between October 25, 2012 and December 9, 2013. The study was designed as a 52-week, multicenter (30 US study sites) study in subjects aged 12 years and older with a documented history of persistent asthma. The study consisted of two parts: Part 1 was a 12-week double-blind treatment period in which subjects were randomized to receive two inhalations QID of either Albuterol MDPI or Placebo MDPI; and Part 2 was a 40-week open-label treatment period in which subjects received open-label Albuterol MDPI prn. The primary objective of the study was to assess the safety of Albuterol MDPI over 52 weeks during the two dosing periods. A major secondary objective was to evaluate the Albuterol MDPI device performance through both periods of the study.

Subjects who qualified to enter the Treatment Period of the double-blind period of the study were randomized into one of two treatment arms as follows:

- Albuterol MDPI 90 mcg/inhalation, 2 inhalations QID
- Placebo MDPI 0 mcg/inhalation, 2 inhalations QID

Subjects that continued to the open-label period of the study were provided an Albuterol MDPI 90 mcg/inhalation, 2 inhalations Q4-6hrs prn. Subjects were provided a ProAir HFA MDI as a back-up rescue inhaler.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 12 years or older
    - Diagnosis of persistent asthma and current use of an MDI containing a short-acting β2-adrenergic agonist
    - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study
- 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
- Women who were pregnant or nursing
- Use of any protocol-prohibited medications

The following medications were allowed during the study but were withheld as pre-specified in the protocol prior to and during study site visits requiring spirometry assessments:

- Short-acting β_2-adrenergic agonists
- Stable doses of inhaled corticosteroids
- Antihistamines
- Decongestants
- Alcohol
- Foods and beverages containing methyl xanthines or compounds known to inhibit CYP3A4 (e.g., grapefruit)

Subjects were to be on stable doses (≥4 weeks) of inhaled corticosteroids of a low to medium dose defined as the equivalent of ≤500 mcg/day of fluticasone proprionate throughout the study. Prohibited concomitant medications included omalizumab, β2-adrenergic antagonists, MAO inhibitors, oral β-adrenergic agonists, and non-K^+-sparing diuretics.

The focus of Study ABS-AS-307 was evaluation of the device performance; consequently, efficacy was not assessed. Descriptive statistics were used to assess study variables and safety outcomes.

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.

There were three amendments made to the protocol that largely detailed clarifications to protocol procedures. Additionally, the Sponsor had notified the Division of a change in the analyses due to an inadvertent omission from the statistical analysis plan that stated a logistic regression analysis would be used to model the percent of 12% and 15% responders. 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 337 subjects with persistent asthma were randomized into the study. A total of 45 (13%) subjects withdrew from the study with similar numbers of subjects withdrawing from the Albuterol MDPI (n=22) and Placebo MDPI (n=23) treatment arms. The most frequent reason for withdrawal was Withdrawal of Consent, which occurred in nine Albuterol MDPI-treated subjects and 13 Placebo MDPI-treated subjects.

There were six (2%) subjects with ≥1 protocol violations: five Placebo MDPI-treated subjects and one Albuterol MDPI-treated subject. One subject was allowed to continue in the study despite being initially randomized to the Placebo MDPI group but received Albuterol MDPI at Treatment Visit 4. 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 37 years of age (range 12-76 years), white (75%), and with a greater proportion of females than males (64% vs. 36%, respectively). Approximately equal proportions of children aged 12 to 17 years were enrolled in the Placebo MDPI (n=19) and Albuterol MDPI (n=25) treatment arms.

5.3.5.7 Study ABS-AS-308

Study ABS-AS-308, entitled "*A Prospective, Open-Label Assessment of Albuterol Spiromax DPI Dose Counter*", was conducted between May 22, 2013 and September 12, 2013. The study was designed as a five-week, multicenter (30 US study sites), phase 3, open-label study in subjects aged 4 years and older who have been diagnosed with persistent asthma. Eligible subjects were evaluated as a screening visit that was followed by a seven to 14 day Run-in Period. Subjects with adequate Albuterol MDPI device dosing technique who were ≥90% compliant with dosing and diary completion for the Run-in Period were subsequently enrolled into the open-label study during which time subjects received Albuterol MDPI 180 mcg (two 90 mcg/inhalation) BID using the to-be-marketed Albuterol MDPI with dose-counter. The primary objective of the study was to assess the performance of the Albuterol MDPI dose-counter with "typical" patient use.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria

  - Male or female subjects aged 4 years or older
  - Diagnosis of asthma or COPD with symptoms of bronchoconstriction requiring the use of short-acting β_2-agonists
  - Asthma/COPD treatment regimen had remained stable for ≥4 weeks

- Major Exclusion Criteria

  - History of life-threatening asthma or COPD defined as an asthma or COPD 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
  - Culture-documented or suspected respiratory infection
  - Women who were pregnant or nursing
  - Current treatment with a long-acting β_2-agonist as monotherapy
  - Uncontrolled hypertension
  - History or current evidence of any concurrent medical disorder
  - Use of any protocol-prohibited medications

Concordance between subject-reported Albuterol MDPI counter readings and subject-reported dose cycles recorded in the daily diaries was assessed and the discrepancies were classified into four categories:

- Dose cycle "not count" (undercount): subject completed a full dose cycle but the counter display did not display count down
- Dose cycle overcount: subject completed a full dose cycle but the counter display decreased by more than one count
- Count unknown dose cycle: for a given session recorded in the daily diary, the immediately preceding entry in the diary occurred on the same day or the previous day, and the MDPI dose counter had advanced between dosing sessions although the patient has not knowingly executed a dose cycle
- Count up unknown dose cycle: for a given session recorded in the daily diary, the immediately preceding entry in the diary occurred on the same day or the previous day, and the MDPI device had counted upwards between dosing sessions and the patient had not knowingly executed a dose cycle

The primary endpoint of Study ABS-AS-308 assessed Dose Cycle "not count" given that it is the most clinically important dose counter discrepancy.

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 317 subjects at 30 study sites in the US were enrolled in the study. The Per-Protocol population (n=253) included all data from randomized subjects who were deemed compliant (≥90% of doses) and did not experience a major protocol violation. There were no formal amendments to the protocol. One subject was lost to follow-up and unable to be included in the Safety population. A total of 16 (5%) subjects were terminated early from the study with the most frequent reasons being protocol violations (n=6), "other reasons" (n=4), and withdrawal of consent (n=3).

There were six (2%) subjects with ≥1 protocol violations, all of them due to receiving protocol-prohibited medications. The overall number and type of protocol violations 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 51 years of age (range 5-88 years), white (85%), and with a greater proportion of females than males (56% vs. 44%, respectively). A total of 44 children aged 4 to 11 years were enrolled in the study.

6 Review of Efficacy

Efficacy Summary

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-101 and -201 demonstrated similar single-dose efficacy and safety profiles of Albuterol MDPI and ProAir HFA in subjects age 12 years and older who were diagnosed with persistent asthma. Both studies met their primary endpoints assessing FEV_1 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.

Studies ABS-AS-301 and -304 both met their primary endpoints demonstrating that subjects treated with Albuterol-MDPI 180 mcg experienced clinically meaningful and statistically significant increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ compared to placebo-treated subjects over the 12-weeks of the controlled period of the studies. Analyses of the secondary endpoints of both studies were supportive and together the data confirm the known effectiveness of albuterol in subjects with asthma.

Subjects treated with Albuterol-MDPI 180 mcg in Study ABS-AS-302 demonstrated a significant effect on exercise-induced bronchospasm compared to subjects treated with Placebo-MDPI. Treatment with Albuterol-MDPI prior to exercise reduced the post-

exercise percentage fall in FEV_1 to 6% compared to 22% for placebo-treated subjects. An alternative way to put these findings into perspective is that 84% of Albuterol MDPI-pretreated subjects experienced a <10% decrease in FEV_1 compared to only 16% of placebo-pretreated subjects, which translates into a clinically significant benefit. Together, these data demonstrate a clinically meaningful benefit of Albuterol MDPI 180 mcg for patients diagnosed with exercise-induced bronchospasm.

Studies ABS-AS-307 and -308 were used assess the performance of the new MDPI device. The performance of the MDPI device was a secondary objective in Study ABS-AS-307 and the primary objective of Study ABS-AS-308. The data from these studies demonstrated that the total number of device-related complaints was low and that the proposed MDPI device with integrated counter performed adequately and in a reliable manner with a minimal rate of dose cycle "undercounting".

Overall, the data support the claim that pharmacologic therapy with Albuterol MDPI 180 mcg effectively treats and prevents bronchospasm in patients 12 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 12 years of age and older with reversible obstructive airway disease
- Prevention of exercise-induced bronchospasm in patients 12 years of age and older

6.1.1 Methods

As discussed in Section 5.2, data from studies ABS-AS-101, -201, -301, -302, and -304 were used to support the efficacy of Albuterol MDPI for treating patients with persistent asthma and exercise-induced asthma. These five 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 exercise-induced bronchospasm.

6.1.2 Demographics

Baseline demographics and disease characteristics for each of the five 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 well-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 five 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 withdrawal of consent. On the whole, the patterns of patient disposition did not appear to favor or disfavor used of Albuterol-MDPI.

6.1.4 Analysis of Primary Endpoint

6.1.4.1 Study ABS-AS-101

The primary efficacy endpoint of Study ABS-AS-101 was the baseline-adjusted FEV_1 at 30 minutes after each of the five cumulative doses. Each of the five cumulative doses demonstrated improvements from baseline FEV_1 30-minutes after dosing demonstrating the effectiveness of both albuterol products (Table 4). Although not statistically

significant, the changes from baseline FEV_1 were lower for the Albuterol MDPI treatment arm compared to the ProAir HFA treatment arm with the differences ranging between 36 mL to 66 mL. These differences are not considered to be clinically meaningful.

Table 4. Study ABS-AS-101: ΔFEV1 after Cumulative Dosing*

Cumulative Dose (mcg)	ΔFEV_1 mL (N)		Treatment Difference (90% CI)
	HFA	MDPI	HFA – MDPI
90	426 (46)	383 (46)	43 (-25, 110)
180	505 (45)	439 (46)	66 (-2, 133)
360	573 (46)	528 (46)	45 (-22, 112)
720	611 (46)	563 (46)	48 (-19, 115)
1440	649 (45)	613 (46)	36 (-31, 103)

*source: Division of Biometrics Statistical Review, Table 5. HFA: ProAir HFA; MDPI: Albuterol MDPI

6.1.4.2 Study ABS-AS-201

The primary efficacy endpoint of Study ABS-AS-201 was the baseline-adjusted FEV_1 $AUEC_{0\text{-}6hr}$ measured in L*hr. Subjects treated with any dose of Albuterol MDPI or ProAir HFA demonstrated significant increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ compared to placebo-treated subjects (Table 5). Although not statistically significant, a general dose-response relationship can be appreciated between the 90 mcg and 180 mcg doses of Albuterol MDPI and ProAir-HFA treatment arms, which demonstrated similar degrees of bronchodilation compared to placebo-treated subjects. These data demonstrate a clinical benefit for the use of albuterol, delivered via MDPI or HFA, in subjects with persistent asthma.

Table 5. Study ABS-AS-201: ΔFEV1 AUC0-6hr*

Treatment Arm	$\Delta AUC_{0\text{-}6hr}$ L*hr (N)	Treatment Difference Drug-Placebo (p-value)
Placebo	0.244 (69)	-
Albuterol-MDPI 90 mcg	1.214 (70)	0.970 (<.0001)
ProAir-HFA 90 mcg	1.124 (70)	0.88 (<.0001)
Albuterol-MDPI 180 mcg	1.394 (68)	1.15 (<.0001)
ProAir-HFA 180 mcg	1.328 (68)	1.083 (<.0001)
*source: Adapted from the Division of Biometrics Statistical Review, Table 8		

6.1.4.3 Studies ABS-AS-301 and ABS-AS-304

The primary efficacy endpoint for Studies ABS-AS-301 and -304 was the baseline-adjusted ΔFEV_1 $AUC_{0\text{-}6hr}$ measured in L*hr over the 12-week treatment period. Subjects treated with Albuterol-MDPI 180 mcg demonstrated significant increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ compared to placebo-treated subjects over the 12-weeks of the controlled period in both studies (Table 6). Albuterol-MDPI-treated subjects demonstrated an increase of 0.83 L/hr and 0.92 L/hr compared to Placebo-treated subjects over the 12-week periods of Studies ABS-AS-301 and -304, respectively. These data represent a clinically meaningful effect for subjects with persistent asthma treated with Albuterol-MDPI 180 mcg compared to placebo-treated subjects.

Table 6. Studies ABS-AS-301, -304: ΔFEV1 AUC0-6hr Over 12 Weeks*

Study	$\Delta AUC_{0\text{-}6hr}$ L*hr (N)		Treatment Difference (p-value)
	Albuterol-MDPI 180 mcg (n)	PBO (n)	
301	1.107 (78)	0.28 (79)	0.827 (<.0001)
304	1.300 (75)	0.384 (84)	0.917 (<.0001)

*source: Adapted from the Division of Biometrics Statistical Review, Table 14

6.1.4.4 Study ABS-AS-302

Subjects treated with Albuterol-MDPI 180 mcg demonstrated a significant effect on exercise-induced bronchospasm compared to subjects treated with Placebo-MDPI (Table 7). Treatment with Albuterol-MDPI prior to exercise reduced the post-exercise percentage fall in FEV_1 to 6% compared to 22% for placebo-treated subjects. These data demonstrate a clinically meaningful benefit of Albuterol-MDPI 180 mcg for patients diagnosed with exercise-induced bronchospasm.

Table 7. Study ABS-AS-302: Maximum Exercise-Induced Percent Decrease in FEV1*

Treatment Arm	Max % Decrease FEV_1 (N)	Treatment Difference Drug-Placebo (p-value)
Placebo	22 (38)	-
Albuterol-MDPI 180 mcg	6 (38)	-16 (<.0001)
*source: Adapted from the Division of Biometrics Statistical Review, Table 17		

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Study ABS-AS-101

Increases in mean plasma glucose levels were observed at all 15-minute post-dose timepoints for Albuterol-MDPI and ProAir-HFA with minimal increases at albuterol doses <360 mcg (Table 8). Differences between albuterol treatments were typically small (1 to 2 mg/dL) at all timepoints and while the maximum change from baseline (3.8 mg/dL) was statistically significant, the magnitude of the difference is not considered clinically meaningful.

Table 8. Change from Baseline in Plasma Glucose (mg/dL)

Cumulative Dose (mcg)	mg/dL (N)		Treatment Difference (90% CI)
	HFA	MDPI	HFA – MDPI
90	0.2 (36)	0.3 (37)	0.1 (-2.4, 2.6)
180	1 (35)	0.1 (36)	-0.9 (-3.5, 1.6)
360	2.6 (34)	1.8 (36)	-0.9 (-3.4, 1.7)
720	4 (34)	5.9 (37)	1.9 (-0.6, 4.3)
1440	9.1 (35)	11.4 (36)	2.3 (-0.3, 4.8)
*source: Sponsor's Clinical Study Report ABS-AS-101			

No substantial changes in mean plasma potassium levels were observed for either Albuterol-MDPI or ProAir-HFA at any dose level remaining <0.10 mEq/L at all 15-minute post-dose timepoints (Table 9).

Table 9. Change from Baseline in Plasma Potassium (mEq/L)

Cumulative Dose (mcg)	mEq/L (N)		Treatment Difference (90% CI)
	HFA	MDPI	HFA – MDPI
90	0 (37)	0.1 (37)	0.1 (-0.1, 0.2)
180	0.1 (35)	0.1 (36)	0 (-0.1, 0.1)
360	0.1 (35)	0 (36)	-0.1 (-0.2, 0)
720	0.1 (37)	-0.1 (37)	-0.1 (-0.2, 0.1)
1440	0.3 (36)	-0.4 (35)	-0.1 (-0.2, 0)
*source: Sponsor's Clinical Study Report ABS-AS-101			

Subjects treated with Albuterol-MDPI and ProAir HFA demonstrated small increases in heart rate as doses greater than 360 mcg (Table 10). Observed differences in mean heart rate between treatment arms were less than five beats per minute at all 15-minute

post-dose timepoints. None of the observed differences are considered clinically meaningful.

Table 10. Change from Baseline in Heart Rate (bpm)

Cumulative Dose (mcg)	bpm (N)		Treatment Difference (90% CI)
	HFA	MDPI	HFA – MDPI
90	-0.8 (38)	0.7 (38)	1.5 (-1.1, 4)
180	-0.5 (38)	-0.7 (38)	-0.2 (-2.8, 2.3)
360	-0.1 (38)	0.4 (38)	0.5 (-2, 3)
720	3.1 (38)	4.6 (38)	1.5 (-1.1, 4)
1440	7.5(38)	12 (38)	4.5 (2, 7.1)
*source: Sponsor's Clinical Study Report ABS-AS-101			

Analysis of QT_C intervals, systolic blood pressure, and diastolic blood pressure demonstrated similar changes between albuterol treatments that were overall small and not clinically meaningful (data not shown).

6.1.5.2 Study ABS-AS-201

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. In his review, Dr. Abugov notes that the values generated from his analysis differed slightly from that of the Sponsor (within four to five mL), but on the whole demonstrated that there were no statistically significant differences between products or doses (Table 11). The reviewer is referred to Dr. Abugov's review for a detailed discussion of his analysis for assessing the time of onset for Albuterol-MDPI and ProAir-HFA.

Table 11. ΔFEV1 Five Nominal Minutes Post-Dose, Albuterol versus Placebo

ΔFEV_1 mL (N)					Difference (P-Value)			
M180	H180	M90	H90	P	M180-P	M90-P	H180-P	H90-P
289 (68)	304 (68)	273 (68)	270 (70)	28 (69)	262 (<.0001)	245 (<.0001)	276 (<.0001)	242 (<.0001)
*source: Adapted from the Division of Biometrics Statistical Review, Table 10								

6.1.5.3 Study ABS-AS-301 and ABS-AS-304

As shown in Table 12, changes from baseline in ΔFEV_1 $AUC_{0\text{-}6hr}$ for Albuterol-MDPI relative to placebo at each timepoint during the 12-week controlled period did not demonstrate a statistically significant difference between timepoints.

Table 12. ΔFEV1 AUC0-6hr, by Study Day, Albuterol MDPI versus Placebo

Study	Visit	$\Delta AUC_{0\text{-}6hr}$ L*hr (N)		Difference	
		M180	P	M180-P	95% CI
301	D1	1.584 (78)	0.516 (79)	1.068 (<.0001)	(0.675, 1.460)
	W1	0.992 (78)	0.261 (78)	0.731 (<.0001)	(0.407, 1.055)
	W12	0.745 (77)	0.064 (77)	0.681 (<.0001)	(0.375, 0.986)
304	D1	1.633 (75)	0.581 (84)	1.053 (<.0001)	(0.56, 1.545)
	W1	1.146 (74)	0.374 (83)	0.772 (0.0004)	(0.352, 1.192)
	W12	1.122 (69)	0.196 (78)	0.926 (<.0001)	(0.57, 1.282)
*source: Adapted from the Division of Biometrics Statistical Review, Table 15					

Subjects treated with Albuterol-MDPI 180 mcg demonstrated a large change from baseline FEV_1 compared to Placebo-MDPI starting five minutes after administration, peaking by two hours, and persisting up to 4-hours (Table 13).

Table 13. ΔFEV1 by Time after Treatment Administration

Time	Study 301			Study 304		
	M180	P	M180-P	M180	P	M180-P
5 min	216 (77)	29 (77)	187 (<.0001)	279 (61)	2 (75)	277 (<.0001)
30 min	270 (76)	45 (76)	225 (<.0001)	318 (66)	36 (75)	282 (<.0001)
1 hour	257 (76)	28 (74)	229 (<.0001)	346 (65)	34 (75)	312 (<.0001)
2 hour	193 (75)	16 (76)	176 (<.0001)	272 (64)	52 (74)	220 (<.0001)
3 hour	111 (76)	3 (72)	107 (<.0001)	210 (65)	45 (75)	165 (<.0001)
4 hour	49 (75)	-12 (74)	61 (0.0225)	132 (65)	35 (76)	96 (0.0027)
5 hour	7 (76)	-16 (75)	23 (0.3892)	78 (66)	34 (73)	44 (0.1686)

*source: Adapted from the Division of Biometrics Statistical Review, Table 16

6.1.5.4 Study ABS-AS-302

Approximately 84% of subjects pretreated with Albuterol-MDPI were observed to have <10% decrease in FEV_1 following an exercise challenge compared to 16% of placebo-treated subjects (Table 14). The Sponsor used a simplified logistic analysis with treatment as the only fixed effect when the originally planned analysis failed to

converge; however, Dr. Abugov performed the Sponsor's originally planned analysis, using all fixed effects, using SAS proc GLIMMIX and demonstrated that the results of his analysis confirmed those provided by the Sponsor.

Table 14. Percentage of Patients with Maximum Exercise-Induced Percent Decrease in FEV1 <10%

Percentage of Patients Protected (N)		Difference (P-Value)
M180	P	M180-P
84	16	68
(38)	(38)	(<.0001)

*source: Adapted from the Division of Biometrics Statistical Review, Table 18

6.1.6 Other Endpoints (Device Function)

Given the change in formulation and device, the Agency considered Albuterol MDPI to be a new drug and new device for regulatory purposes. Consequently, the Sponsor assessed the performance of the device both directly and indirectly in Studies ABS-AS-307 and -308. The performance of the MDPI device was a secondary objective in Study ABS-AS-307 and the primary objective of Study ABS-AS-308.

6.1.6.1 Study ABS-AS-307

The total number of inhalers utilized during Study ABS-AS-307 was examined for performance issues over the time periods of Weeks 0-12, Weeks 13-52, and Weeks 0-52. As shown in Table 15, the overall study compliance for was high for both Albuterol-MDPI (92%) and Placebo-MDPI (97%) treatment arms was high with compliance defined as ≥80% of compliance with dosing.

Table 15. Summary of Study Drug Compliance

Category	Placebo-MDPI N=170 (%)	Albuterol-MDPI N=168 (%)
<60%	0	3 (2)
60-80%	4 (2)	9 (5)
80-100%	165 (97)	154 (92)
>100%	1 (<1)	2 (1)
*source: Sponsor's Clinical Study Report ABS-AS-307, Table 11		

A total of 672 Placebo-MDPI and 647 Albuterol-MDPI inhalers were used in the double-blind phase of study and 1252 Albuterol-MDPI inhalers were used during the open-label phase. A total of six patients reported seven broken inhalers of which two inhalers were run through washing machines, one inhaler was broken during an altercation, and one report of a broken mouthpiece cover. Fourteen inhalers reported to be malfunctioning were returned to the Sponsor and subjected to further testing. Nine of the malfunctions were caused by intentional or accidental abuse of the inhaler with broken/dislocated mouthpiece covers (n=4) and exposure to extreme moisture (n=5). Five of the reported malfunctions involved subjects' perceived perception of not receiving a dose of drug. All five of the devices were examined for device functionality and demonstrated that all five of the inhalers were mechanically functional and correctly delivered the specified albuterol dose.

Although Albuterol-MDPI was used on an 'as-needed" basis during the open-label phase of the study, subjects were still provided with a ProAir-HFA Inhaler as back-up rescue medication. Consequently, the use of the ProAir-HFA inhaler was used as an indirect measure to monitor the functioning of the Albuterol-MDPI device. Analysis of the data showed that two subjects reported ≥14 puffs daily of their ProAir-HFA inhaler. Subject 10148020 had failed to obtain a replacement Albuterol-MDPI during their clinic visit and Subject 10148002 experienced an asthma exacerbation that was not relieved

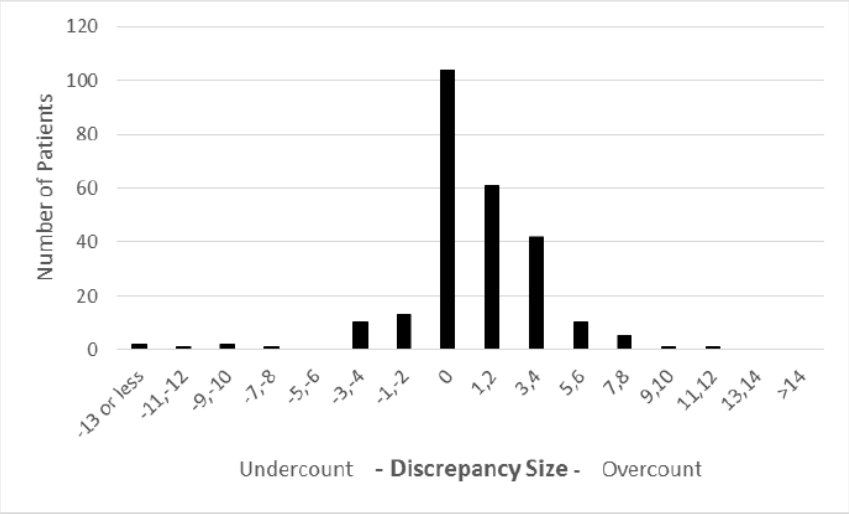
via standard treatment regimens and, as per the protocol, was terminated early from the study.

In summary, the total number of device-related complaints was low with 14 subjects reporting complaints, the majority of which were attributed to intentional/accidental abuse of the inhaler or exposure to extreme moisture. The results from this study demonstrate that the proposed MDPI device performed adequately and in a reliable manner.

6.1.6.2 Study ABS-AS-308

Study ABS-AS-308 was designed to evaluate the device dose-counter reliability over an eight-week period. The primary population for dose counter analyses was the Per-Protocol population which consisted of the 253 subjects who completed the study and received at least 180 of 200 (≥90%) schedule doses accounting for a total number of subject-reported dose cycles of 49,454. The overall rate of discrepancies for this population was 5 per 200 dose cycles with dose cycle overcount being the most commonly reported dose-counter error. The number of inhaler discrepancies reported per patient ranged from 0 to 47 in the Per-Protocol population. The total discrepancy size per inhaler was centered on a difference of zero with a greater tendency for overcounting rather than undercounting for inhalations (Figure 4). The absolute value of the total discrepancy size per inhaler for the Per-Patient population was 2 ± 3 (mean ± SE).

Figure 4. Categorization of Total Discrepancy Size per Inhaler



*source: Sponsor's Clinical Study Report ABS-AS-308, Figure 1.

The primary endpoint of the study was the incidence of dose cycle "not count" or undercounting of doses delivered as recorded by subjects in the patient diary. The overall rate of discrepancies for dose cycle "not counted" was approximately 2.1 per 200 dose cycles (Table 16).

Table 16. Dose Cycle "Not Count" Dosing Discrepancies per 200 Dose Cycles

	Albuterol-MDPI (N-253)
Total Dose Cycles	49454
Dose Cycle "not count"	506
Dose Cycle "not count"/dose cycles	2.1

*source: Sponsor's Clinical Study Report ABS-AS-308, Table 6

Dose cycle overcount (48%) accounted for the majority of all discrepancies with a 2.6/200 dose cycle rate. "Count unknown" (8%) and "count up unknown" (3%) dose cycles accounted for the next most frequently identified dosing errors.

The highest error rate for all dosing discrepancies occurred in the lowest age group of 4 to 11 years of age (Table 17). The rate of dose cycle "not count" in subjects 4-11 years of age was almost double that of the total Per-Patient population, although the overall rate was still low.

Table 17. Number and Rate of Dosing Discrepancies per 200 dose Cycles

	4-11 Years N=26	**12-64 Years N=59**	**≥65 Years N=35**
Total # Dose Cycle	5037	11542	6860
Total # Discrepancies	206	274	188
Dose cycle "not count"	90	108	72
Dose cycle overcount within dose	93	138	95
Count unknown dose cycle between doses	14	17	17
Count up unknown dose cycle between doses	9	11	4
Discrepancy rate/200 dose cycles	8	5	5
Dose cycle "not count"	4	2	2
Dose cycle overcount within dose	4	2	3
Count unknown dose cycle between doses	1	<1	1
Count up unknown dose cycle between doses	<1	<1	<1

*source: Sponsor's Clinical Study Report ABS-AS-308, Table 9

A total of three (1%) subjects from the Intent-to-Treat population reported non-counter-related device issues: two subjects reported impact damage and one subject reported difficulty inhaling through the device and closing the mouthpiece cover.

Overall, the results of Study ABS-AS-308 demonstrated that the Albuterol-MDPI device with integrated dose counter was reliable and functioned accurately in the clinical setting of twice daily dosing over seven weeks. Most importantly, the low rate of discrepancies for the primary endpoint of dose cycle "not count" was low suggesting that dose undercount with the device is minimal.

6.1.7 Subpopulations

No significant subgroup effects on efficacy were seen based on sex, race, age, or geographic region. The reader is referred to Dr. Abugov'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. Abugov's statistical review for a discussion of persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

The reader is referred to Dr. Abugov'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.

A total of 10 clinical studies in adult and adolescent patients have been completed and support the safety of Albuterol MDPI. Overall, 1456 patients were included in the clinical program of who 1120 received treatment with Albuterol MDPI. Among patients treated with Albuterol MDPI, 840 were treated with the inhaler proposed for marketing. The primary safety data is derived from clinical studies that were wholly conducted in the USA at geographically diverse locations.

No deaths occurred during the clinical program for Albuterol MDPI. A total of 15 subjects reported serious adverse events which included 13 subjects treated with Albuterol MDPI and two subjects treated with placebo. Similarly, only 10 subjects discontinued a clinical study due to an adverse event (Albuterol MDPI (n=8), Placebo MDPI (n=2)). The majority of the serious adverse events and adverse events resulting in discontinuation were not related to study drug. The most commonly reported adverse events (reported in ≥5% of subjects) included upper respiratory tract infection, nasopharyngitis, and headache. In general, the percentage of subjects reporting adverse events was either similar between treatment arms or slightly greater in placebo-treated subjects. For labeling purposes, adverse events experienced ≥1% of of

Albuterol MDPI-treated subjects and greater than placebo-treated subjects was back pain, pain, gastroenteritis, sinus headache, urinary tract infection.

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 12 years of age and older with obstructive airway disease or exercise-induced bronchospasm.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from Studies ABS-AS-301, -304, and -307 provide the pivotal safety information for Albuterol MDPI. All three studies were designed to include a 12-week double-blind treatment period utilizing the MDPI device proposed for marketing. These studies allow 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, Studies ABS-AS-301 and -304 were 12-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group studies in subjects aged 12 years and older 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 12-weeks.

Study ABS-AS-307 was designed as a 52-week, multicenter study in subjects aged 12 years and older with a documented history of persistent asthma. The study consisted of two parts: Part 1 was a 12-week double-blind treatment period in which subjects were randomized to receive two inhalations QID of either Albuterol MDPI or Placebo MDPI; and Part 2 was a 40-week open-label treatment period in which subjects received open-

label Albuterol MDPI as needed. The primary objective of the study was to assess the safety of Albuterol MDPI over 52 weeks during the two dosing periods.

Supportive safety data are provided from Studies ABS-AS-101, -201, -302, and -308, which will be discussed separately from the pooled analyses in the relevant safety sections. Additionally, safety data from Albuterol MDPI-related studies involving the (b) (4) and salbumatol will be discussed separately under Section 7.7.

Study ABS-AS-101 was a phase 1, multicenter, randomized, double-blind, double-dummy, cumulative-dose, crossover study in adult subjects (18 to 45 years of age) with persistent asthma. The primary objective of the study was to compare the efficacy of inhaled albuterol MDPI and inhaled ProAir HFA after a cumulative dose of 1440 mcg administered as 1+1+2+4+8 inhalations of 90 mcg per inhalation.

Study ABS-AS-201 was designed as a multicenter, randomized, double-blind, double-dummy, single-dose, five-treatment, 10-sequence, placebo-controlled, crossover comparison of the bronchodilator response to Albuterol MDPI and ProAir HFA in subjects age 12 and older with persistent asthma.

Study ABS-AS-302 was designed as a phase 3, single-dose, randomized, double-blind, placebo-controlled, two-treatment, two-sequence, two-way crossover, multicenter study of Albuterol MDPI compared to Placebo MDPI in male and female subjects age 12 to 50 years of age with a documented history of exercise-induced asthma. Safety data from this study was not pooled for use in the primary safety analysis given the difference in patient population and relatively small numbers of subjects enrolled (n=38).

(b) (4) (b) (4)

(b) (4)

Studies IX-100-076 and IX-101-076 were conducted with salbutamol (albuterol) MDPI that utilized a higher dose (100 mcg of albuterol base). Study IX-100-076 was a randomized, single blind, placebo/active-controlled, five-treatment, cumulative dose (maximum eight inhalations), five-period crossover study and Study IX-101-076 was an open-label study of three increasing single doses of salbutamol-MDPI with no comparator.

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 the pivotal clinical studies 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 specifically assessed in Study ABS-AS-101 given the suprapharmacologic doses of albuterol administered. In Study ABS-AS-302, laboratory evaluations were only performed at the screening

visit; 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

ECG recordings for Studies ABS-AS-101, -302, -306, -307 ECG were centralized and standardized across all study subjects. The corrected QT interval (QTc) was calculated using Bazett's formula [QTc(B)] and Fridericia's formula for each ECG. Any ECG finding that was judged as a clinically meaningful change compared to a baseline value was considered an adverse event. A Lead II ECG was measured 30 minutes prior to the first dose and 15 and 30 minutes after each dose for Study IX-100-076.

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

Safety data from Studies ABS-AS-301, -304, and the 12-week controlled period of Study ABS-AS-307 were pooled for the primary analysis of safety as these studies allowed for the direct comparison of adverse events between treatment with Albuterol MDPI and placebo in subjects using the to-be-marketed device.

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-201, which administered doses of Albuterol MDPI 90 mcg and 180 mcg, did not demonstrate a correlation between drug dose and increased adverse events. An increased frequency of adverse events was recognized but only at suprapharmacologic doses in Study ABS-AS-101, which administered cumulative doses of Albuterol MDPI up to 1440 mcg. 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.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

None.

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.

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

None.

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

A total of 15 subjects reported a serious adverse event during the Albuterol MDPI development program (Albuterol MDPI (n=13) and Placebo MDPI (n=2)).

During the controlled period of Studies ABS-AS-301, -304, and -307 a total of two of 321 (<1%) Albuterol MDPI-treated subjects and one of 333 (<1%) Placebo MDPI-treated subjects reported a serious adverse event. The reported serious adverse events were as follows:

- Albuterol MDPI (n=2)
  - Enterocolitis
  - Pharyngeal abscess
- Placebo MDPI (n=1)
  - Spontaneous abortion (first trimester)

A total of seven subjects experienced a serious adverse event during the open-label period of Study ABS-AS-307 that included a single case each of cellulitis, pancreatic carcinoma, gastrointestinal carcinoma, atrial fibrillation, papillary thyroid cancer, asthma, and kidney stone.

Two subjects in Study ABS-AS-308 (atrial fibrillation; rash) and two subjects in Study ABS-AS-306 (asthma; rectal adenocarcinoma) reported serious adverse events. No serious adverse events were reported in Studies ABS-AS-101, -201, or -302 or the two studies conducted with salbutamol MDPI.

In summary, the rates of serious adverse events were balanced between treatment arms in the three controlled periods of Studies ABS-AS-301, -304, and -307. Furthermore, the types of serious adverse events reported do not appear to be related to the known safety profile of albuterol or lactose. Overall, these data do not identify a new safety signal associated with the use of Albuterol MDPI.

7.3.3 Dropouts and/or Discontinuations

A total of 10 subjects discontinued from study treatment due to adverse events during the Albuterol MDPI development program (Albuterol MDPI (n=8) and Placebo MDPI (n=2)).

During the controlled period of Studies ABS-AS-301, -304, and -307 a total of three of 321 (<1%) Albuterol MDPI-treated subjects and two of 333 (<1%) Placebo MDPI-treated subjects were withdrawn from study drugs due to adverse events.

Four subjects experienced an adverse event that led to discontinuation from the study during the open-label period of Study ABS-AS-307. These adverse events were listed in the serious adverse event section above and included pancreatic carcinoma, gastrointestinal carcinoma, papillary thyroid cancer, and asthma exacerbation.

No discontinuations due to adverse events were reported in Studies ABS-AS-101, -201, -302, (b) (4)

One subject from Study ABS-AS-308 (sinusitis) and four subjects from the salbutamol MDPI studies (coughing, hayfever, angioedema, asthma exacerbation) were withdrawn from studies due to an adverse event.

In summary, the rates of discontinuations were balanced between treatment arms in the three controlled periods of Studies ABS-AS-301, -304, and -307. These data do not identify a new safety signal associated with the use of Albuterol MDPI.

7.3.4 Significant Adverse Events

The Sponsor performed additional analyses assessing adverse events potentially associated with the use of β_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.

The incidence of all events was very low with only headache and sinus headache being reported ≥1% of Albuterol MDPI-treated subjects, with approximately equal numbers of patients reporting sinus headaches (~1% in each treatment arm) and a lower proportion of Albuterol MDPI subjects having reported headaches compared to Placebo MDPI subjects, 4% vs. 6%, respectively. Other adverse events in subjects treated with Albuterol MDPI occurred at either the same frequency or less than that of placebo-treated subjects.

Hypersensitivity reactions have been reported following the administration of albuterol sulfate presenting as urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. Four mild hypersensitivity reactions (urticaria (n=2), face swelling

(n=1), pruriitis (n=1)) were reported during the controlled periods of Studies ABS-AS-301, -304, or -307 in subjects treated with Albuterol MDPI. No reports of Albuterol MDPI-associated hypersensitivity reactions were reported during the open-label period of Study ABS-AS-307 or in the remainder of the Sponsor's studies. A single case of anaphylaxis was reported in the Placebo MDPI treatment arm during Study ABS-AS-307. 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.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Eighty-nine of 711 (13%) subjects treated with Placebo MDPI during the run-in period of Studies-ABS-AS-301, -304, and -307 reported an adverse event. No subjects experienced a serious adverse event or were discontinued from the study during this period of the Study.

A total of 128 of 321 (40%) Albuterol MDPI-treated subjects reported an adverse event compared to 166 of 333 (50%) of Placebo MDPI-treated subjects during the 12-week controlled period of the three studies (Table 18). Approximately 98% of 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 18. Summary of Adverse Events (ITT)

Category	Number (%) of Patients	
	Albuterol MDPI N=321	**Placebo MDPI N=333**
Patients ≥1 Adverse Event	128 (40)	166 (50)
Discontinuations due to adverse event	3 (<1)	2(<1)
Adverse Event Severity		
Mild	70 (22)	72 (22)
Moderate	53 (17)	84 (25)
Severe	5 (2)	10 (3)
Serious Adverse Events	2 (<1)	1 (<1)

MDPI: multipledose dry powder inhaler; source: ISS, Table 10

The most common adverse events were reported in the infections/infestations and respiratory, thoracic, and mediastinal disorders System Organ Classes with a greater proportion of Placebo-treated subjects reporting adverse events compared to Albuterol MDPI-treated subjects (31% vs. 23% and 11% vs. 9%, respectively; Table 19).

Table 19. Adverse Events by System Organ Class

System Organ Class	Number (%) of Patients	
	Albuterol MDPI N=321	Placebo MDPI N=333
Patients ≥1 Adverse Event	128 (40)	166 (50)
Infections/Infestations	75 (23)	104 (31)
Respiratory, Thoracic, Mediastinal	28 (9)	35 (11)
Nervous System	20 (6)	30 (9)
Gastrointenstinal System	20 (6)	25 (8)
Musculoskeletal System	17 (5)	22 (7)
General Disorders	13 (4)	5 (2)
Injury, Poisoning, & Procedural	11 (3)	21 (6)
Skin and Subcutaneous Tissue	6 (2)	8 (2)
MDPI: multipledose dry powder inhaler; source: ISS, Table 11		

Upper respiratory tract infection was the most commonly reported adverse event, which was reported in a greater proportion of subjects treated with placebo compared to albuterol (Table 20). Nasopharyngitis and headache were the only other adverse events reported in ≥5% of subject in either treatment arm. Overall, no new safety signals associated with Albuterol MDPI were identified in subjects during the controlled periods of Studies ABS-AS-301, -304, and -307.

Table 20. Adverse Events by Preferred Term in >1% of Subjects

System Organ Class	Number (%) of Patients	
	Albuterol MDPI N=321	Placebo MDPI N=333
Patients ≥1 Adverse Event	128 (40)	166 (50)
Upper respiratory tract infection	31 (10)	38 (11)
Nasopharyngitis	17 (5)	21 96)

Headache	13 (4)	19 (6)
Oropharyngeal pain	11 (3)	13 (4)
Cough	10 (3)	13 (4)
Sinusitis	8 (2)	14 (4)
Back pain	6 (2)	4 (1)
Influenza	5 (2)	13 (4)
Pain	5 (2)	2 (<1)
Gastrointestinal viral	4 (1)	3 (<1)
Sinus headache	4 (1)	3 (<1)
Urinary Tract Infection	4 (1)	3 (<1)

MDPI: multipledose dry powder inhaler; source: ISS, Table 12

In general, the frequency and type of adverse events reported during the open-label period of Study ABS-AS-307 was similar to that reported in the controlled periods of subjects treated with Albuterol MDPI during the three controlled studies.

One subject from each treatment arm of Study ABS-AS-302 reported an adverse event with the Placebo-treated subject experiencing a migraine and the Albuterol MDPI-treated subject reported bradycardia.

Eighty-five of 316 (27%) subjects reported ≥1 adverse event during Study ABS-AS-308 in which patients were treated with Albuterol MDPI twice daily for five or seven weeks. The most frequently occurring adverse events were headache (n=8), sinusitis (n=7), cough (n=6), upper respiratory infection (n=6), and Nasopharyngitis (n=4).

Approximately equal proportions of subjects in Study ABS-AS-306 reported ≥1 adverse event with 36% of albuterol-treated subjects compared to 35% of placebo-treated subjects. The most frequently reported adverse events in both treatment groups were upper respiratory tract infections (6% vs. 7%, respectively).

In Study ABS-AS-101, ≥1 adverse event was reported by 15 of 46 (33%) subjects treated with Albuterol MDPI and by 13 of 46 (28%) subjects treated with ProAir HFA. The majority of adverse events were considered to be treatment-related (Albuterol MDPI (n=11); ProAir HFA (n=10)), which is expected given the supratherapeutic doses administered in this study. The most frequently reported adverse events ≥5% of subjects) were tremor, palpitations, and headache. Nine of 71 (13%) subjects in

StudyABS-AS-201 reported ≥1 adverse event (Albuterol MDPI 90 mcg (n=3), Albuterol MDPI 180 mcg (n=3), ProAir HFA 180 mcg (n=2), and Placebo MDPI (n=2)). All adverse events were reported a mild or moderate in intensity. Adverse events were infrequent and balanced between treatment arms in both salbutamol MDPI studies. The types and frequency of adverse events were consistent with the safety profile seen in the Albuterol MDPI studies.

7.4.2 Laboratory Findings

No hematology, clinical chemistry, or urinalysis assessments were performed in Studies ABS-AS-201, -301, -302, or -304. Study ABS-AS-307 analyzed blood samples at the screening visit, Week 12, and Week 52 (or early discontinuation). No clinically meaningful changes from baseline were identified during any period of the study. Greater than 85% of values remained within normal ranges for both treatment arms. Similarly, data from Study ABS-AS-306 and the two salbutamol MDPI studies did not show clinically significant changes from baseline in either of the two treatment arms.

In the cumulative dose study ABS-AS-101, mean changes from baseline in hematology and clinical chemistry values were generally small and similar between treatment arms. Four subjects reported five adverse events related to laboratory measurements following treatment with either Albuterol MDPI or ProAir HFA: decreased serum potassium (n=2), increased serum potassium (n=1), increased bilirubin (N=1), and increased serum LDH (n=1). Abnormal laboratory values were similar between

treatment arms and no clinical intervention was required to treat the abnormal laboratory values.

Overall, the data did not identify a clinically significant signal regarding changes in laboratory values in subjects treated with Albuterol MDPI.

7.4.3 Vital Signs

There was a small tendency for subjects administered Albuterol MDPI to have a small increase in blood pressure and heart rate compared to placebo for Study ABS-AS-301. Similarly, in Study ABS-AS-304 Albuterol MDPI-treated subjects demonstrated a slight increase in heart rate and blood pressure with Albuterol compared to placebo. Overall, the increases were minor, with a maximum mean increase of about 4 mmHg seen for systolic blood pressure at 3 hours on Day 8.

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 is vital signs.

In Study ABS-AS-304, four subjects randomized to Albuterol MDPI treatment (increased systolic blood pressure (n=2), increased diastolic blood pressure (n=1), and an increase in both systolic and diastolic blood pressure (n=1)) and three subjects assigned to Placebo MDPI treatment (increased systolic blood pressure (n=1), increased diastolic blood pressure (n=1), and an increase in both systolic and diastolic blood pressure (n=1)) had clinically significant findings on vital signs.

Vital signs were measured at screening, after the end of the 12-week double-blind phase, and at Week 52 after the end of the 40-week open- label phase when all patients were treated with Albuterol MDPI. Overall, there were no clinically meaningful trends in mean changes from baseline for any vital signs variables; however, clinically significant changes in vital signs were reported in three Albuterol MDPI-treated subjects (increased systolic blood pressure (n=2), tachycardia (n=1)) during the controlled period and five patients during the open-label phase.

In Study ABS-AS-302, heart rate increased with exercise in both treatment groups but there was no apparent effect on heart rate for either treatment arm at screening or treatment visits. Overall, there was no apparent effect on systolic or diastolic blood pressure, respiratory rate, or temperature.
Mean vital signs at the end of study visits for Study ABS-AS-306 were similar to those recorded at screening and randomization. Similarly, the majority of vitals signs were within the predefined reference ranges at all study visits for Study ABS-AS-101 and overall there were no clinically significant changes from baseline.

In Study ABS-AS-201 vital signs were performed at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after completion of dosing. The maximum changes from baseline in systolic and diastolic blood pressures were small and similar to placebo for all albuterol treatment arms. The maximum changes from baseline in heart rate were small and similar to placebo for all albuterol treatment arms.

In Study IX-100-076, Salbutamol MDPI administration resulted in statistically significant increases in heart rate at 15 and 30 minutes after treatment compared to placebo. Sixteen patients experienced an abnormal heart rate on one or more occasions; abnormal heart rate occurred in each treatment period, including placebo, and at the pre-dose assessments.

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-307, ECGs were collected at the screening visit, Week 12, and Week 52 (or early termination). There were no clinically relevant findings in mean values at any time point in either the placebo or Albuterol MDPI treatment groups. No patient had a QTc interval length greater than 500 msec at any time point. There was no shift in ECG from normal to abnormal during the controlled period of the study; however, ten Placebo MDPI-treated subjects and eight Albuterol MDPI subjects had shifts to abnormal that were not deemed clinically relevant. During the open-label phase, one subject's ECG developed a new anterior T-wave inversion on day 366 without a cardiovascular adverse event. The clinical significance of this event is uncertain.

Shifts in ECG from pre-exercise to post-exercise, rated as normal or abnormal, and were common in both placebo and Albuterol MDPI treatment groups during Study ABS-AS-302. Among the 38 subjects in this study, 12 placebo and nine Albuterol MDPI subjects were reported to have abnormal ECGs pre-exercise, of which five and three subjects, respectively, remained abnormal post-exercise. Additionally, ten placebo and 11 Albuterol MDPI subjects changed from normal ECG pre-exercise to abnormal postexercise. One case was judged clinically significant. QTc interval findings at pre-dose and 30 minutes post-dose were analyzed using Bazetts and Fridericias corrections. Changes were comparable in the two treatment groups, with QTcB showing a 15% to 17% increase from pre-dose to post-exercise and QTcF showing essentially no change. No patient had a QTcB or QTcF >450 msec.

In Study ABS-AS-306, no Albuterol MDPI-treated subjects had an abnormal, clinically relevant ECG at the end of study visit while four patients in the placebo group had an abnormal, clinically relevant ECG at the end of study visit.

In Study ABS-AS-101, ECG was performed five minutes prior to the first dose and at 15 minutes post-dosing following each of the first four cumulative doses, and, following the fifth dose at 15 and 30 minutes and 1, 2, 3, and 4 hours. Overall, there were minimal changes in QTc intervals for either Albuterol MDPI or ProAir HFA at dose levels below 360 mcg. There were small expected increases in QTc intervals for both Albuterol MDPI and ProAir HFA at dose levels above 360 mcg that were similar for both products. Differences between treatment arms were small and not clinically significant. There was an overall mean increase in QTcB up to the administration of the last cumulative dose (1440 mcg) of each treatment, after which mean QTcB decreased in both treatment groups but did not return to baseline by the 4-hour post-dose time point in either treatment group. Similar results were seen for QTcF, except that QTcF did not decrease appreciably during the 4-hour observation period following administration of the final cumulative dose. As expected, overall changes from baseline with high doses of albuterol were potentially clinically significant for both mean QTcB and mean QTcF; however, the observed differences between treatments were small and not clinically meaningful.

Two patients had abnormal ECG results during treatment with placebo and VENTOLIN DISKHALER and VENTOLIN ACCUHALER during the salbutamol MDPI study IX-100-076, but the events were mild and considered not drug related.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Non-applicable.

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.

7.5.2 Time Dependency for Adverse Events

Not applicable.

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 pleacebo-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 β_2-adrenergic receptor agonists, β-blockers, diuretics, digoxin, and monoamine oxidase inhibitors or tricyclic antidepressants.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not evaluated in this NDA.

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. (b) (4) . 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 clinical program for Albuterol MDPI. Results from Study ABS-AS-101, which administered cumulative doses of Albuterol MDPI up to 1440 mcg, demonstrated expected pharmacodynamic effects primarily at suprapharmacologic doses that were consistent with the mechanism of action of albuterol. None of the effects were considered to be clinically significant.

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 β2-agonists.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day Safety Update

A 120-day safety update report was submitted on August 29, 2014 and provided additional information from the time of the NDA submission through July 23, 2014. There was limited data provided since the studies included in this application were completed at the time of submission. Of note, a 24-year-old woman had become pregnant during the course of Study ABS-AS-307 and delivered a healthy baby via vaginal delivery after the study was completed.

Additional data included in the 120-day safety update included safety data from the Sponsor's ongoing and completed pediatric studies, which will not be discussed in this review; however, the data did not identify new safety signals.

7.7.2 Device Performance

Review of the Albuterol MDPI device with integrated dose counter is discussed in Section 6.1.6.2.

8 Postmarketing Experience

Albuterol MDPI (RespiClick) is not approved for use for any indication anywhere in the world. Consequently, there is no postmarketing experience with the product.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Major clinical labeling recommendations:

- **Section 2.2:** change to "*For prevention of exercise-induced bronchospasm…*"
  - Study ABS-AS-302 demonstrated prevention of exercise-induced bronchospasm

- **Section 8.4:** delete sentences (b)(4)
  - Insufficient data to support claim. Study ABS-AS-308 was an open-label study assessing device reliability that enrolled five subjects aged 5-11 years of age.

- **Section 14:** delete (b) (4)
  - Primary endpoint results are adequately represented by the two graphs included in the label

- **Section 14:** delete sentence (b)(
  - Inadequately controlled and statistically analyzed data

- **Section 14**: delete [redacted] (b) (4)
  - Inadequately controlled data

- **Section 14**: delete [redacted]
  - Study not designed to assess comparability

- **Section 14**: delete [redacted] (b) (4)
  - Study not designed to assess comparability and unapproved patient population (4-11 year old children)

9.3 Advisory Committee Meeting

Following the initial review and discussion of the application, the review team determined Albuterol MDPI to be efficacious in adult patients 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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/s/

KEITH M HULL
01/28/2015

NIKOLAY P NIKOLOV
01/28/2015
I concur.