U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205-636
Supplement #:	004
Drug Name:	ProAir Respiclick (Albuterol Multi-Dose Dry Powder Inhaler)
Indication(s):	For the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients four to eleven years old
Applicant:	Teva Branded Pharmaceutical Products, R&D, Inc.
Date(s):	Received Date: 06/29/2015
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Review Priority:	Standard
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Keywords: NDA review, Clinical Studies

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1 EXECUTIVE SUMMARY

The initial NDA 205,636 from Teva Branded Pharmaceutical Products, R&D, Inc. (Teva) for albuterol multi-dose dry powder inhaler (MDPI) in adult and adolescent patients (12 years of age and older) with asthma and exercise-induced bronchoconstriction (EIB) was approved on March 31, 2015. Teva has submitted the current supplemental NDA to extend the labeling indication to include pediatric patients in the 4 to 11 years age range, inclusive. This submission includes three clinical trials to examine the efficacy and safety of albuterol MDPI for the treatment and prevention of bronchospasm with reversible obstructive airway disease in pediatric patients aged 4 to11 years.

The pediatric program demonstrated statistically significant benefit of albuterol MDPI for the treatment or prevention of bronchospasm in patients with asthma 4 to 11 years of age, inclusive, as measured by lung function. Study ABS-AS-202 demonstrated that both 90 mcg and 180 mcg doses of albuterol MDPI improved FEV_1 area under the curve 0 to 6 hours post dose (AUC_{0-6}), in both percentage predicted and original FEV_1 for the pediatric patient population. Study ABS-AS-303 demonstrated that the 180 mcg four times a day (QID) dose of albuterol MDPI improved both percentage predicted FEV_1 ($PPFEV_1$) AUC_{0-6} and FEV_1 AUC_{0-6} over a 3-week treatment period when compared with placebo. There was no efficacy assessment in the phase 1 pediatric study ABS-AS-102 so this study was not discussed in this review.

In addition, these studies provided supporting data to characterize the short-acting β_2-adrenergic receptor agonist (SABA) treatment timing profile, in terms of peak FEV_1 and 15% or 12% improvement in $PPFEV_1$ from baseline.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class, Indication and History of Drug Development

Albuterol is a short-acting β_2-adrenergic receptor agonist (SABA) bronchodilator. Orally inhaled albuterol delivered in aerosol formulation through the metered-dose inhaler (MDI) has been the standard care for bronchospasm. There are several products of albuterol MDI on the U.S. market, among them, Teva's ProAir HFA (albuterol sulfate hydrofluoroalkane). Teva's albuterol sulfate multi-dose dry powder inhaler (MDPI) was developed to be pharmacologically comparable to ProAir HFA while using a novel inhalation-driven actuation technique to improve administration over the conventional MDI device.

The original application of albuterol MDPI was approved on March 31, 2015 in the US for treatment or prevention of bronchospasm with reversible obstructive airway disease and prevention of exercised-induced bronchospasm (EIB) in patients 12 years of age and older. In the original application, albuterol MDPI was designed to be dosed in the same dose (equivalent to 90 mcg of albuterol base per actuation) and at the same frequency (2 inhalations every 4 to 6 hours) as ProAir HFA. The current submission pursues approval for the same indication in pediatric patients of 4 to 11 years old.

Table 1: Relevant applications

Drug Name	NDA Number	Company	Dose	Indication
ProAir HFA (albuterol sulfate inhalation aerosol)	21-457	Teva Specialty Pharmaceuticals, LLC, Horsham, PA	Albuterol Sulfate Inhalation Aerosol 90 mcg	Treatment for the acute relief of bronchospasm and for the prevention of EIB
ProAir RespiClick (albuterol sulfate MDPI)	205-636	Teva Specialty Pharmaceuticals, LLC, Horsham, PA	Albuterol MDPI 180 mcg	Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. Prevention of exercise-induced bronchospasm.

EIB = exercised-induced bronchospasm; HFA = hydrofluoroalkane; MDPI = multi-dose dry powder inhaler

2.1.2 Pediatric Clinical Program

This pediatric supplemental NDA includes three trials to examine the efficacy and safety of albuterol MDPI for the treatment and prevention of bronchospasm with reversible obstructive airway disease in pediatric patients aged 4 -11 years (Table 1). Study ABS-AS-102 (study 102) is a phase 1 pharmacokinetic (PK), pharmacodynamics (PD) and safety study to compare albuterol MDPI and ProAir HFA. Study ABS-AS-202 (study 202) is a phase 2 crossover efficacy and safety study to evaluate the efficacy of albuterol MDPI and ProAir HFA at 2 dose levels relative

to placebo. Study ABS-AS-303 (study 303) is a phase 3 study to evaluate the repeat-dose efficacy of albuterol MDPI relative to placebo.

For efficacy evaluation, this review will focus on efficacy studies 202 and 303.

Table 2: List of all pediatric studies (pediatric asthma patients 4-11 years old)

Study	Type of Study	Phase and Design	Treatment Period	Treatment Arms	# of Subjects per Arm
ABS-AS-102	PK, PD, and Safety	Phase 1, OL, CO	Single doses	Albuterol MDPI 180 mcg inhalation, ProAir HFA 180 mcg by inhalation	16 screened, 15 enrolled
ABS-AS-202	Efficacy & Safety	Phase 2 MC, R, DB, DD, PC, single-dose, 5-treatment, 5-way CO	Single doses	Albuterol MDPI 90 or 180 mcg inhalation, ProAir HFA 90 or 180 mcg by inhalation, placebo	102 screened, 61 randomized, 57 completed
ABS-AS-303	Efficacy & Safety	Phase 3, 3-wk, MC, R, DB, PC, repeat dose	3 wks	Albuterol MDPI 180 mcg QID, placebo QID by inhalation	377 screened, 185 randomized (albuterol 94, placebo 92), 162 completed (albuterol 80, placebo 82)

CO = crossover; DB = double-blind; DD = double-dummy; MC = multicenter; OL = open-label; PC = placebo-controlled; PD = pharmacodynamics; PK = pharmacokinetics; QID = 4 times a day; R = randomized; wk = week

The pediatric clinical program does not include clinical trial to demonstrate efficacy in EIB for children ages 4 to 11 years, which is planned to be extrapolated based on data from both the adolescent and adult albuterol MDPI EIB trials and ProAir HFA pediatric program.

2.2 Data Sources

Data for all three trials were provided by the applicant and are currently located at:

\\cdsesub1\evsprod\NDA205636\0031\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis quality were adequate in this submission. During the review process, I identified inconsistencies in analysis data structure between study ABS-AS-202 and study ABS-AS-303. An information request to the applicant resolved issues concerning the derived analysis datasets.

The results in the tables within this review were generated by me to validate applicant's results; applicant's corresponding table numbers in CSR and the reviewer's SAS program names are given in the footnotes to facilitate cross validation.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study 202

The primary objective of study 202 was to evaluate the efficacy of albuterol MDPI and ProAir HFA at 2 dose levels (90 mcg, 180 mcg) relative to placebo (Table 3) in patients 4 to 11 years of age with persistent asthma. As the intent of the study was to demonstrate the comparability of Albuterol MDPI and ProAir HFA inhalers, the evaluated dosages were selected on the approved pediatric doses of ProAir HFA.

Table 3: Treatment groups in Study 202

Code	Number	Treatment
A	1	Albuterol MDPI 90 mcg (administered as 1 actuation of 90 mcg of albuterol base/actuation ex-mouthpiece) orally inhaled
B	2	Albuterol MDPI 180 mcg (administered as 2 actuations of 90 mcg of albuterol base/actuation ex-mouthpiece) orally inhaled
C	3	ProAir HFA 90 mcg (administered as 1 actuation of 90 mcg of albuterol base/actuation ex-mouthpiece) orally inhaled
D	4	ProAir HFA 180 mcg (administered as 2 actuations of 90 mcg of albuterol base/actuation ex-mouthpiece) orally inhaled
E	5	Placebo MDPI + Placebo ProAir HFA 0 mcg of albuterol base orally inhaled

Study 202 was a phase 2 multicenter, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 5-treatment, 5-period, 10-sequence, 5-way crossover study in pediatric patients aged 4 to 11 years, inclusive, with persistent asthma.

The 10 treatment sequences were generated according to a Williams design in 2 Latin square blocks of 5 sequences each. Table 4 illustrates the 10 treatment sequences. In the Williams design, each treatment follows every other treatment the same amount of times such that the design is balanced for first order carryover effects. Of the 102 patients screened for enrollment, 61 patients were randomized to one of the ten treatment sequences with 6 patients each in 9 of the sequences and 7 patients in one sequence. The trial was conducted in 14 clinical sites in the US.

Table 4: Treatment sequences

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	Placebo	HFA 90	MDPI 180	MDPI 90	HFA 180
2	MDPI 180	Placebo	HFA 180	HFA 90	MDPI 90
3	HFA 180	MDPI 180	MDPI 90	Placebo	HFA 90

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
4	MDPI 90	HFA 180	HFA 90	MDPI 180	Placebo
5	HFA 90	MDPI 90	Placebo	HFA 180	MDPI 180
6	HFA 180	MDPI 90	MDPI 180	HFA 90	Placebo
7	MDPI 90	HFA 90	HFA 180	Placebo	MDPI 180
8	HFA 90	Placebo	MDPI 90	MDPI 180	HFA 180
9	Placebo	MDPI 180	HFA 90	HFA 180	MDPI 90
10	MDPI 180	HFA 180	Placebo	MDPI 90	HFA 90

Source: Sponsor's Study ABS-AS-202 SAP Table 1.

To maintain blinding of the treatment (MDPI and MDI) and dose (90 mcg and 180 mcg), a double-blinded and double-dummy procedure was used by providing 4 inhalers to each patient for each treatment application (2 MDPIs and 2 MDIs).

For each of the five treatment period, spirometry data was collected at 30 minutes prior and again within 5 minutes prior to the commencement of study drug administration, and at 5, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes after completion of study drug administration.

Due to the natural development of lung function, especially during childhood, it results in heterogeneity of FEV_1 data among pediatric patients (4 to 11 years of age under this submission), $PPFEV_1$ based on age, sex and height of each patient was used rather than measured FEV_1 in this pediatric program. The primary efficacy endpoint was the baseline-adjusted percent-predicted FEV_1 versus time curve over 6 hours after dosing ($\Delta PPFEV_1$ AUC_{0-6}[%*hour]). For each treatment, baseline $PPFEV_1$ was calculated from the average of the two $PPFEV_1$ values obtained before treatment. If only one before treatment FEV_1 determination was available, this value was taken as the baseline. The $\Delta PPFEV_1$ AUC_{0-6} was calculated using the linear trapezoidal rule.

The secondary efficacy variable was the baseline-adjusted FEV_1 AUC_{0-6}[L*hour]). The AUC computation was similar to that for the primary efficacy endpoint.

To fully characterize the rate, time to on-set and duration of bronchodilation for this SABA, two responder efficacy variables were also defined following SABA convention to profile the drug effect. Treatment effect in terms of responder rate was assessed together with its corresponding time in minutes to on-set and duration in hours of response. The response was defined as greater than or equal to 15% and 12%, separately, increase in baseline $PPFEV_1$ within 30 minutes after treatment.

Additionally, baseline-adjusted maximum FEV_1 or $PPFEV_1$ within 6 hours after treatment and time in minutes to maximum $PPFEV_1$ data were collected. Table 5 illustrates this set of efficacy endpoints. This review focused on the $PPFEV_1$ endpoint and investigated corresponding responder rate and its related time variable analyses.

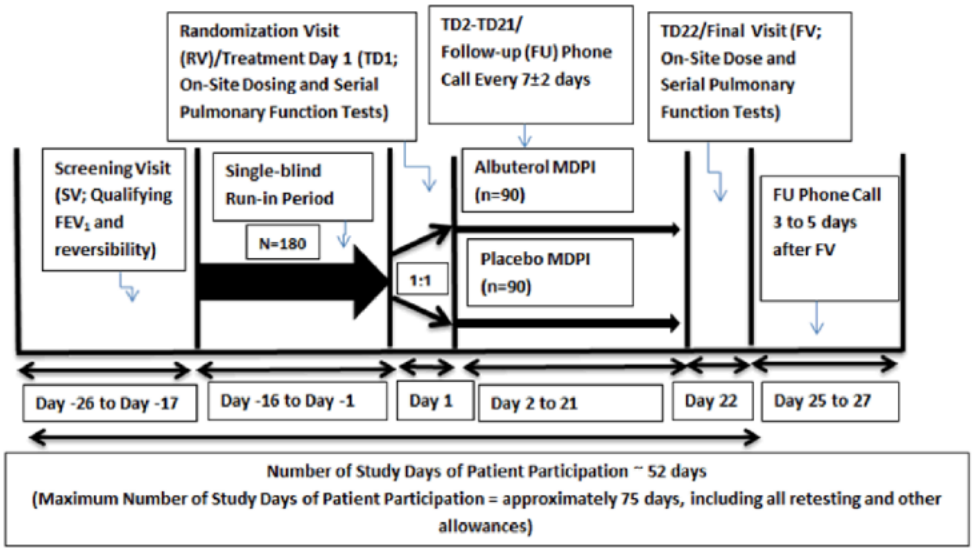
Table 5: Additional efficacy variables

	Maximum (within 6 hours post dose)		15% Response (within 30 minutes post dose)			12% Response (within 30 minutes post dose)		
	Value	Time to	Rate	Time to	Duration	Rate	Time to	Duration
$PPFEV_1$	✓	✓	✓	✓	✓	✓	✓	✓
FEV_1	✓	NA						

3.2.1.2 Study 303

The primary objective of study 303 was to evaluate the repeat-dose efficacy of albuterol MDPI relative to placebo in pediatric patients with asthma. Study 303 was a phase 3, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group, 8-week (3-week double-blind treatment) study in male and female patients 4 to 11 years of age, inclusive, with asthma. Figure 1 displays the study schema.

Figure 1: Study schema for Study ABS-AS-303



Source: Sponsor study 303 protocol Figure 1.

After the screening / run-in period of 14 days, patients started the treatment period of 3 weeks with visits on treatment day 1 (TD1) and treatment day 22 (TD22). TD22 was also the final visit; the study ended with a telephone followed up on days 3 to 5 after first dose.

On TD1 and TD22, serial FEV_1 measurements were taken at the same time points as in study 202. Study 303 is a repeated-dose study.

The primary efficacy endpoint was the baseline-adjusted $PPFEV_1$ AUC_{0-6}[%*hour] over the 3-week double-blind treatment period. The primary analysis time point was the entire treatment period from TD1 to TD22. The secondary efficacy endpoint was the baseline-adjusted peak expiratory flow (PEF) AUC_{0-6}[L*hour] over the 3-week double-blind treatment period.

The SABA bronchodilation onset and duration characteristics were assessed similarly as in study 202 except that in study 202 the maximum post dose value and responder assessments was based on change in $PPFEV_1$ and in study 303 they were based on change in FEV_1.

3.2.2 Statistical Methodologies

3.2.2.1 Study 202

The primary analysis model for $PPFEV_1$ AUC_{0-6} and FEV_1 AUC_{0-6} was a mixed-effect analysis of variance with fixed effects of baseline, sequence, treatment group, and period and a random effect for the patient within sequence. For the primary and secondary efficacy variable and for each treatment dosage group, comparison between that active treatment arm and placebo was derived from the model by contrast.

The mean difference between each active treatment arm and placebo was tested in a sequential order to control type I error rate: MDPI 180 mcg vs. placebo, MDPI 90 mcg vs. placebo, HFA 180 mcg vs. placebo and HFA 90 mcg vs. placebo. The tests were each conducted as 2-sided with significance level of 0.05.

A mixed logistic regression model was used to compare the rate of responders between each active group and placebo. The model included fixed effects of treatment, period, and a random effect for subject. For the responders, arithmetic summary statistics for time to response and response duration were derived.

The primary analyses were conducted based on the full analysis population (FAS), which was defined as all randomized subjects who received at least one dose of study medication, had a baseline assessment, and had at least one post-baseline assessment. In FAS, treatment was assigned based on the treatment randomized regardless of actual treatment received.

3.2.2.2 Study 303

The primary analysis model for the primary and secondary efficacy endpoints was the mixed model repeated measure (MMRM) with $PPFEV_1$ AUC_{0-6} or FEV_1 AUC_{0-6} over the 3-week treatment period as the response, fixed effects of baseline $PPFEV_1$ AUC_{0-6} or FEV_1 AUC_{0-6} at each study day, treatment group, study day, and study day by treatment interaction. An

unstructured covariance matrix was assumed for the repeated measures. Analysis population and analyses of the other efficacy variables were similar to the corresponding ones in study 202.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 202

There was no pattern of imbalance in terms of patient demographics and baseline characteristics among the 10 treatment sequences (Appendix A).

There were five patients in study 202 that either received treatments that were different from planned treatments or discontinued study early so not all five of the treatments were administered. Of the 4 patients who discontinue study drug early, the reported reason is all "other".

Table 6: Early withdrawals and patients who received different from assigned treatment

Subject ID	Planned Treatment Sequence	Actual Treatment Sequence
AS_202_10576001	CAEDB	CAED
AS_202_10576002	ADCBE	ADDCE
AS_202_10576008	ECBAD	EC
AS_202_10576012	DBAEC	DB
AS_202_10578002	BEDCA	B

Source: Reviewer's Analysis

3.2.3.2 Study 303

Among the 377 screened patients, 186 patients were randomized to enter the study. There was no pattern of imbalance of the demographic and baseline characteristics among the treatment groups (Appendix A). Also, there was no notable difference between the two treatment groups in patient disposition (Appendix B). About 87% of the randomized patients completed the study.

3.2.4 Results and Conclusions

3.2.4.1 Study 202

To evaluate the efficacy of albuterol MDPI versus placebo in the heterogeneous pediatric population, a percent-predicted correction of FEV_1 was used as the primary efficacy endpoint. Analysis results showed that, in terms of both $PPFEV_1$ AUC_{0-6}[%*hour] and FEV_1 AUC_{0-6} [L*hour], all the albuterol active treatment groups demonstrated significant bronchodilator effect over placebo (Table 7, Table 8). The results for responder and related analyses with 15% increase are the only additional secondary endpoints proposed by applicant to be included in the labeling and are presented in this review (Table 9, Table 10).

In study 202, 27 of 61 patients treated with albuterol MDPI 180 mcg achieved a 15% increase in FEV_1 within 30 minutes post-dose. The median time to onset was 8.0 minutes, and the median duration of effect as measured by a 15% increase was approximately 3 hours.

Table 7: Statistical analysis of baseline-adjusted $PPFEV_1$ AUC_{0-6}[%*hour] (FAS)

Statistic	Placebo	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
n	59	58	59	59	59
Treatment					
Mean±SE	25.4±6.25	46.6±6.27	48.0±6.26	37.9±6.25	49.1±6.26
95% CI	12.94, 37.81	34.12, 59.07	35.56, 60.39	25.43, 50.30	36.61, 61.50
Active-Placebo					
Mean±SE		21.2±4.87	22.6±4.87	12.5±4.85	23.7±4.85
95% CI		11.62, 30.81	13.00, 32.20	2.93, 22.05	14.13, 33.23
P-value		<0.0001	<0.0001	0.0107	<0.0001

Source: Sponsor CSR Table 9, Reviewer program Alb_202_PPFEVAUC.sas

Table 8: Statistical analysis of baseline-adjusted FEV_1 AUC_{0-6}[L*hour] (FAS)

Statistic	Placebo	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
n	59	58	59	59	59
Treatment					
Mean±SE	0.48±0.14	0.88±0.14	0.93±0.14	0.74±0.14	0.93±0.14
95% CI	0.20, 0.76	0.60, 1.16	0.65, 1.20	0.46, 1.02	0.65, 1.21
Active-Placebo					
Mean±SE		0.40±0.10	0.45±0.10	0.26±0.10	0.45±0.10
95% CI		0.21, 0.59	0.26, 0.64	0.08, 0.45	0.26, 0.64
P-value		<0.0001	<0.0001	0.0062	<0.0001

Source: Sponsor CSR Table 10, Reviewer program Alb_202_FEVAUC.sas

Table 9: **Statistical analysis of responder rate based on 15% increase in baseline-adjusted FEV_1 within 30 minutes (FAS)**

Statistic	Placebo	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
Treatment					
Mean estimated rate±SE	0.10±0.04	0.43±0.09	0.43±0.09	0.30±0.08	0.37±0.09
95% CI	0.01, 0.18	0.24, 0.61	0.25, 0.62	0.14, 0.47	0.19, 0.54
Active-Placebo					
Mean estimated rate±SE		0.33±0.09	0.34±0.09	0.21±0.08	0.27±0.09
95% CI		0.15, 0.51	0.15, 0.52	0.05, 0.37	0.10, 0.45
P-value		0.0006	0.0005	0.0119	0.0027

Source: Sponsor CSR Table 18, Reviewer program Alb_202_Responder.sas

Table 10: Time to onset (minutes) and duration (hours) of 15% increase in baseline-adjusted FEV_1 within 30 minutes (FAS)

Statistic	Albuterol MDPI 90 mcg	Albuterol MDPI 180 mcg	ProAir HFA 90 mcg	ProAir HFA 180 mcg
n	26	27	22	24
Time to onset (minutes)				
Median	8.8	8.0	8.4	8.4
Duration (hours)				
Median	2.8	2.9	1.9	2.3

Source: Sponsor CSR Table 13 and Table16, Reviewer program Alb_202_Duration.sas

3.2.4.2 Study 303

For both the primary efficacy endpoint, baseline-adjusted $PPFEV_1$ AUC_{0-6}, and the secondary endpoint baseline-adjusted PEF AUC_{0-6}, treatment with albuterol 180 mcg showed significant improvement over placebo from the primary analysis (Table 11, Table 12).

Table 11: Statistical analysis of baseline-adjusted $PPFEV_1$ AUC_{0-6}[%*hour] (FAS)

Statistic	Placebo	Albuterol MDPI 180 mcg
n	92	92
Treatment		
Mean±SE	18.7±3.19	43.7±3.20
95% CI	12.41, 25.01	37.41, 50.05
Albuterol - Placebo		
Mean±SE		25.0±4.52
95% CI		16.10, 33.94
P-value		<0.0001

Source: Sponsor CSR Table 11, Reviewer program Alb_303_PPFEVAUC.sas

Table 12: Statistical analysis of baseline-adjusted PEF AUC_{0-6}[L*hour] (FAS)

Statistic	Placebo	Albuterol MDPI 180 mcg
n	92	92
Treatment		
Mean±SE	71.5±10.20	147.9±10.25
95% CI	51.37, 91.66	127.62, 168.08
Albuterol - Placebo		
Mean±SE		76.3±14.47
95% CI		47.76, 104.91
P-value		<0.0001

Source: Sponsor CSR Table 11, Reviewer program Alb_303_PPFEVAUC.sas

The number of patients with a 15% increase in FEV_1 from baseline within 30 minutes after dosing on treatment day 1 (TD1) data was included in the applicant's draft labeling. Table 14 displays my responder analysis results from fitting the data with a mixed effect logistic regression model. Estimated responder rates of a 15% increase after dosing on day 1 was 0.12 and 0.53 for placebo MDPI and albuterol MDPI 180 mcg, respectively. The rate of 15% responders was higher for albuterol MDPI 180 mcg than placebo MDPI on day 1 with an

estimated difference of rate equals 0.41 ($p<0.0001$). For patients who responded with a 15% increase in FEV_1 on day 1, Table 13 and Table 14 display responder rate, median time to onset and median duration of a 15% response. Similar to study 202, these are the only additional secondary endpoints results presented in this review due to applicant's labeling proposal.

Table 13: **Statistical analysis of responder rate based on 15% increase in baseline-adjusted FEV_1 within 30 minutes on TD1 (FAS)**

Statistic	Placebo	Albuterol MDPI 180 mcg
n	92	92
Number (%) of responders with 15% increase	16 (17.4%)	48 (52.2)
Mean estimated rate ± SE	0.12±0.04	0.53±0.07
95% CI	0.04, 0.20	0.39, 0.66
Albuterol - Placebo		
Mean estimated rate ± SE		0.41±0.08
95% CI		0.25, 0.57
P-value		<0.0001

Source: Sponsor CSR Table 21, Reviewer program Alb_303_Responder.sas

Table 14: Time to onset (minutes) and duration (hours) of 15% increase in baseline-adjusted FEV_1 within 30 minutes on TD1 (FAS)

Statistic	Placebo	Albuterol MDPI 180 mcg
n	16	48
Median Time to Onset (minutes)	15.27	5.92
Median Duration (hours)	0.86	0.89

Source: Sponsor CSR Tables 22, 24, Reviewer program Alb_303_Duration.sas

Missing data in study 202 was minimal and was not of concern as it has little impact on the final results. However, study 303 had a notable amount of missing data at TD22. The applicant's primary analysis of the primary efficacy endpoint was based on a MMRM using SAS PROC MIXED based on the FAS data. The maximum likelihood approach used observed data from TD1 and TD22 without imputation for missing data by assuming a missing at random mechanism, which could not be verified. Table 13 summarizes the missing pattern for the $PPFEV_1$ AUC_{0-6} by treatment day and treatment group for the FAS population. The albuterol MDPI arm has a slightly higher rate of dropout than placebo (13% versus 10.9%) at TD22. While the primary results obtained from the primary analysis was the average treatment effect at TD1 and TD22, there was no missing data at TD1, and a closer examination of the disposition data (Table 18) showed no marked imbalance by reasons to withdraw between the two groups.

Table 15: Missing data patterns for the PPFEV$_1$ AUC$_{(0-6)}$ (%*Hour) by Treatment Day and Treatment Group (FAS)

								Group Means			
		TD1		TD22				TD1		TD22	
Treatment	Pattern	Baseline	AUC	Baseline	AUC	Count	Percent	Baseline	AUC	Baseline	AUC
Overall (N=184)	1	X	X	X	X	162	88.0	74.4	30.7	74.3	29.7
	2	X	X	o	o	22	12.0	73.9	43.2		
Placebo (N=92)	1	X	X	X	X	82	89.1	74.7	18.8	75.0	17.7
	2	X	X	o	o	10	10.9	69.4	23.0		
AB MDPI 180 mcg QID (N=92)	1	X	X	X	X	80	87.0	74.1	42.8	73.6	42.0
	2	X	X	o	o	12	13.0	77.7	60.0		

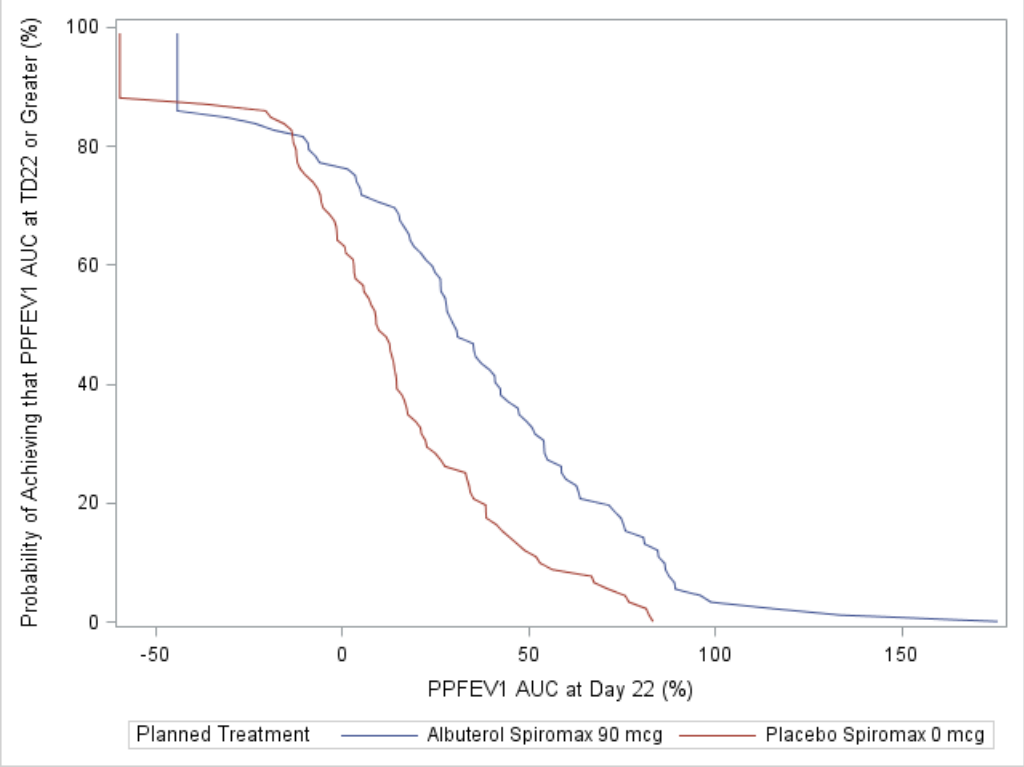
Note: Baseline value is the FEV1 baseline result at each visit that is required for the MMRM analysis of the primary endpoint.
AB = Albuterol; MDPI = Multidose Dry-powder Inhaler; QID = Four times daily; AUC = Area Under the Curve; TD = Treatment Day;
FEV1 = Forced Expiratory Volume in one Second; MMRM = Mixed Model Repeated Measures.
Source listing: Listing 16.2.6.2

Source: Sponsor Study 303 CSR Summary 15.2.47.1

I performed a sensitivity analysis to evaluate the robustness of the primary analysis findings with respect to missing data at TD22 by assuming that the expected value of the measure for those who drop out is not better than that for those who complete the study, the empirical distribution plot approach imputed missing data with the worst outcomes in that treatment group. The empirical distribution functions (Figure 1) show some separation between the placebo and the albuterol MDPI distributions with albuterol MDPI arm has higher proportion of responders compared with placebo using any value of $PPFEV_1$ AUC above 0 as a threshold.

Then a corresponding rank sum statistic of Mann-Whitney-Wilcoxon (MWW) test was calculated on the modified data. The MWW test result ($p<0.0001$) is consistent with the primary analysis result and provides reassurance that the overall conclusion that albuterol MDPI is significantly effective is reliable despite missing data on TD22.

Figure 2: Empirical distribution function for PPFEV1 AUC at Day 22



Source: Reviewer program CPRA_303.sas

3.3 Evaluation of Safety

Safety evaluations for this submission are conducted by the medical reviewer, Keith Hull, M.D.

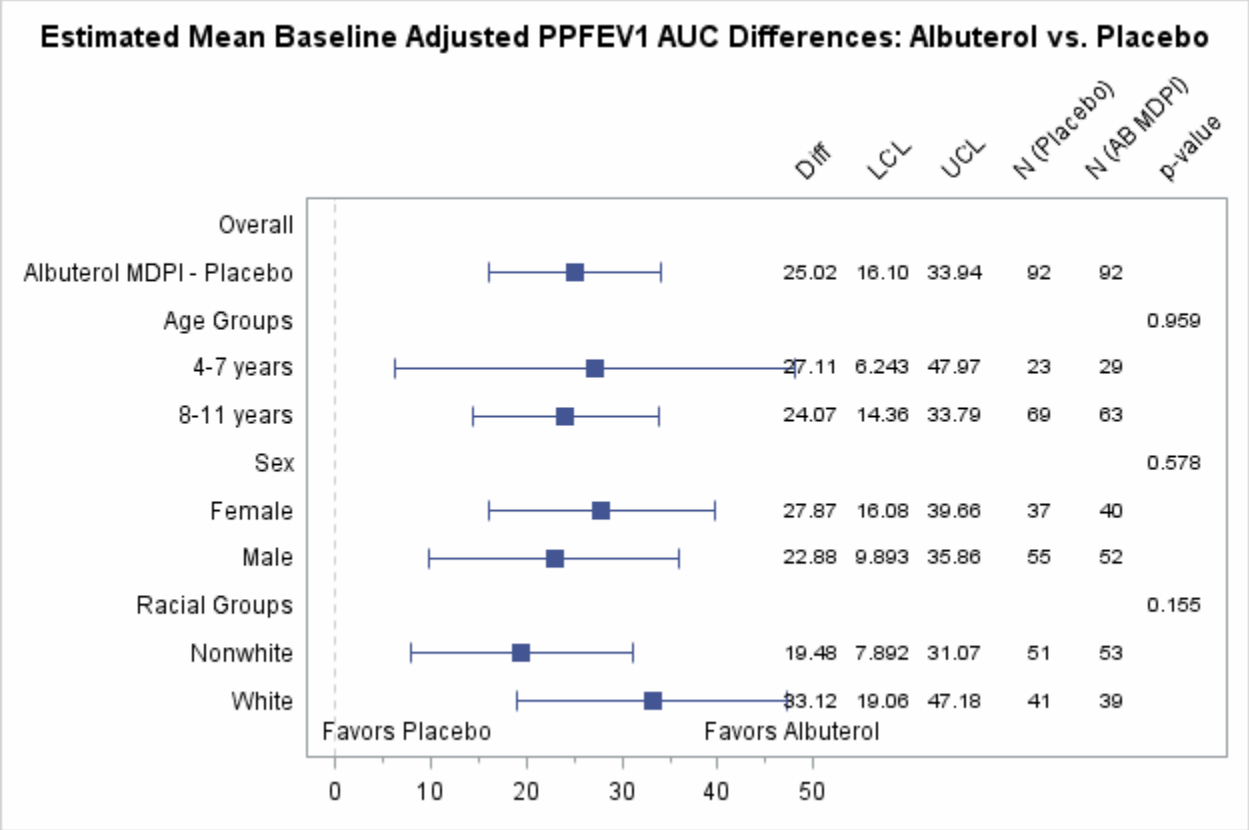
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis was conducted for study 303 with respect to sex, race (White, Non-white) and age (4-7, 8-11) groups to examine the potential of differences in treatment effect among

subgroups. The model was extended from the primary analysis model by adding the subgroup and subgroup by treatment interaction terms. Statistical significance of the interaction terms was examined at the 0.05 level. Figure 3 displays the forest plot together with by subgroup treatment effects estimates, corresponding 95% confidence intervals and treatment subgroup interaction test p-values.

Across the subgroups defined by the three demographic characteristics, treatment differences between albuterol MDPI 180 mcg and placebo were consistent with the primary analysis in overall population. None of these subgroups showed an interaction with treatment effect on the primary efficacy measure.

Figure 3: Subgroup analyses of $PPFEV_1$ AUC (Study ABS-AS-303)



Abbreviations: Diff: Estimated mean difference between the Albuterol MDPI 180 mcg and placebo overall and under each subgroup; LCL: Lower limit of the 95% confidence interval of the mean difference; UCL: Upper limit of the 95% confidence interval of the mean difference; N (Placebo): Number of subjects under placebo; N (AB MDPI): number of subjects under albuterol MDPI 180 mcg.
Source: Reviewer program Albuterol_Forest_303.sas

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The potential influence of missing data on the primary efficacy results was investigated in the statistical results section. There are no other statistical issues that would concern the primary efficacy conclusion.

5.2 Collective Evidence

The collective evidence on lung function from studies 202 and 303 demonstrated efficacy of albuterol MDPI for the treatment and prevention of reversible airway obstruction in pediatric patients 4 to 11 years of age, inclusive.

5.3 Conclusions and Recommendations

The pediatric program demonstrated statistically significant benefit of albuterol MDPI for the treatment or prevention of bronchospasm in patients with asthma 4 to 11 years of age, inclusive, as measured by lung function. Study ABS-AS-202 demonstrated that both 90 mcg and 180 mcg doses of albuterol MDPI improved FEV_1 area under the curve 0 to 6 hours post dose (AUC_{0-6}), in both percentage predicted and original FEV_1 for the pediatric patient population. Study ABS-AS-303 demonstrated that the 180 mcg four times a day (QID) dose of albuterol MDPI improved both percentage predicted FEV_1 ($PPFEV_1$) AUC_{0-6} and FEV_1 AUC_{0-6} over a 3-week treatment period when compared with placebo. There was no efficacy assessment in the phase 1 pediatric study ABS-AS-102 so this study was not discussed in this review.

In addition, these studies provided supporting data to characterize the short-acting β_2-adrenergic receptor agonist (SABA) treatment timing profile, in terms of peak FEV_1 and 15% or 12% improvement in $PPFEV_1$ from baseline.

5.4 Labeling Recommendations

Section 14 clinical studies of the labeling presented the [redacted] (b) (4)

[redacted] (b) (4)

Appendix A: Demographic and Baseline Characteristics

Table 16: Study 202 demographic and baseline characteristics

Demographic	ECBAD #1 (N=6)	BEDCA #2 (N=6)	DBAEC #3 (N=7)	ADCBE #4 (N=6)	CAEDB #5 (N=6)	DABCE #6 (N=6)	ACDEB #7 (N=6)	CEABD #8 (N=6)	EBCDA #9 (N=6)	BDEAC #10 (N=6)	Overall
Age, years	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
Mean ±SD	9.0±2.4	8.8±0.8	8.9±0.7	9.5±2.0	8.7±1.5	9.2±1.5	9.0±1.6	9.2±1.3	8.2±2.2	9.2±2.1	9.0±1.6
Median	10	9	9	10.5	9	9.5	9	9	8.5	10	9
Min, max	6,11	8,10	8,10	7,11	7,11	7,11	7,11	8,11	4,10	5,11	4,11
Sex, n (%)	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
Male	2 (33)	4 (67)	4 (57)	4 (67)	3 (50)	3 (50)	4 (67)	3 (50)	5 (83)	6 (100)	38 (62)
Female	4 (67)	2 (33)	3 (43)	2 (33)	3 (50)	3 (50)	2 (33)	3 (50)	1 (17)	0	23 (38)
Race, n (%)	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
White	1 (17)	1 (17)	5 (71)	0	2 (33)	4 (67)	3 (50)	4 (67)	4 (67)	4 (67)	28 (46)
Black	5 (83)	5 (83)	1 (14)	6 (100)	2 (33)	1 (17)	3 (50)	2 (33)	2 (33)	2 (33)	29 (48)
Other	0	0	1 (14)	0	2 (33)	1 (17)	0	0	0	0	4 (7)
Weight, kg	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
Mean ±SD	43.9±16.5	39.6±8.3	33.1±4.7	47.6±24.6	38.2±15.1	37.6±8.9	36.7±10.9	38.7±13.9	31.5±6.4	36.1±8.6	38.2±12.8
Median	38.8	37.7	32.3	41.5	33.0	40.7	33.0	33.5	32.0	38.6	36
Min, max	29, 72	30.2, 52	27, 39	22, 93.9	28, 68	24.2, 46	28, 57	30, 66	23, 41	19.1, 42	19.1, 93.9
Height, cm	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
Mean ±SD	139.7±16.9	139.7±10.0	138.3±4.7	142.7±13.4	136.3±10.1	140.9±8.26	139.3±8.2	138.5±10.0	132.8±10.5	138.7±13.2	138.7±10.2
Median	136	139.5	139	145.5	134	141.5	137.5	134.5	133.5	144.6	137
Min, max	120, 160	131, 149	132, 145	118, 157	127, 156	131.5, 150	132, 154.5	130, 155	117, 148.5	112, 146	112, 169
BMI, kg/m^2	n=6	n=6	n=7	n=6	n=6	n=6	n=6	n=6	n=6	n=6	N=61
Mean ±SD	22.1±5.44	20.2±3.05	17.2±1.70	22.4±8.35	20.0±4.49	18.9±4.50	18.7±3.79	19.7±4.04	17.8±2.80	18.4±1.94	19.5±4.35
Median	19.7	19.9	17.2	19.8	19.7	18.2	17.9	18.1	17.5	19.0	18.5
Min, max	16.3, 29.6	16.9, 24.7	14.4, 19.9	15.8, 38.1	15.6, 27.9	14.0, 26.4	14.3, 23.9	16.5, 27.5	14.1, 21.8	15.2, 20.2	14.0, 38.1

Source: CSR Table 6, page 57

Table 17: Study 303 demographic and baseline characteristics

Demographic variables	Placebo MDPI (N=92)	Albuterol MDPI (N=94)	Total (N=186)
Age, years			
n	92	94	186
Mean±SD	8.5±1.83	8.3±1.69	8.4±1.76
Median	9	8	9
Min, max	4, 11	4, 11	4, 11
Age group, years, n (%)			
4-7	23 (25.0)	30 (31.9)	53 (28.5)
8-11	69 (75.0)	64 (68.1)	133 (71.5)
Sex, n (%)			
Male	55 (59.8)	52 (55.3)	107 (57.5)
Female	37 (40.2)	42 (44.7)	79 (42.5)
Race, n (%)			
White	41 (44.6)	40 (42.6)	81 (43.5)
Black	48 (52.2)	52 (55.3)	100 (53.8)
American Indian or Alaskan Native	0	1 (1.1)	1 (0.5)
Pacific Islander	0	1 (1.1)	1 (0.5)
Other	3 (3.3)	0	3 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	11 (12.0)	14 (14.9)	25 (13.4)
Not Hispanic or Latino	81 (88.0)	80 (85.1)	161 (86.6)
Weight, kg			
Mean±SD	37.2±13.42	36.1±13.46	36.7±13.41
Median	34.5	34.0	34.0
Min, Max	18.6, 82.8	18.0, 87.1	18, 87.1
Height, cm			
Mean±SD	136.9±12.67	135.2±11.59	136.0±12.13
Median	138.4	134.1	137.1
Min, Max	106.7, 162.6	108.0, 163.8	106.7, 163.8

Source: CSR Table 7, page 67

Appendix B: Disposition of Patients

Table 18: Study 303 disposition of patients table

	Number (%) of patients		
Patient disposition	**Placebo MDPI (N=92)**	**Albuterol MDPI (N=94)**	**Total (N=186)**
Screened	—	—	377
Randomized	92 (100)	94 (100)	186 (100)
Completed	82 (89.1)	80 (85.1)	162 (87.1)
Withdrawn	10 (10.9)	14 (14.9)	24 (12.9)
Adverse event	0 (0.0)	1 (1.1)	1 (0.5)
Withdrawal by subject	1 (1.1)	0 (0.0)	1 (0.5)
Withdrawal by parent/guardian	1 (1.1)	0 (0.0)	1 (0.5)
Protocol violation	2 (2.2)	3 (3.2)	5 (2.7)
Sponsor request	9 (0.0)	1 (1.1)	1 (0.5)
Lost to follow-up	1 (1.1)	4 (4.3)	5 (2.7)
Other	5 (5.4)	5 (5.3)	10 (5.4)
Full analysis set	92 (100)	92 (97.9)	184 (98.9)
Safety population	92 (100)	93 (98.9)	185 (99.5)
Per-protocol set	90 (97.8)	91 (96.8)	181 (97.3)

Source: CSR Table 6, page 66

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/s/

YU WANG
03/23/2016

FREDA COONER
03/23/2016
I concur