CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

Statistical Review

CLINICAL STUDIES

NDA / Sequence Number:	NDA 205636 / Seq 0000
Drug Name:	ProAir RespiClick (albuterol multi-dose dry powder inhaler)
Proposed Indication:	Treatment or prevention of bronchospasm with reversible obstructive airway disease. Prevention of exercise induced bronchospasm
Applicant:	Teva
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1 EXECUTIVE SUMMARY

Teva has submitted one phase 1 trial (study ABS-AS-101), one phase 2 trial (study ABS-AS-201), and three phase 3 trials (studies ABS-AS-301, ABS-AS-302, ABS-AS-304) to evaluate the safety and efficacy of ProAir RespiClick (albuterol sulfate multi-dose dry powder inhaler, 90 mcg per actuation) for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, and the prevention of exercise induced bronchospasm in patients 12 years of age and older.

This submission demonstrates statistically significant benefits of ProAir RespiClick for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, and the prevention of exercise induced bronchospasm. Studies ABS-AS-301 and ABS-AS-304 demonstrated that, compared to placebo, ProAir RespiClick improved FEV_1 $AUC_{0\text{-}6hr}$ and study ABS-AS-302 demonstrated that, compared to placebo, ProAir RespiClick provides a clear reduction in post-exercise bronchospasm.

There was little evidence that efficacy of ProAir RespiClick differed from ProAir HFA, a similar product. Study ABS-AS-101 provided weak evidence that the effect of ProAir RespiClick could be slightly less than comparable doses of ProAir HFA; however that result was contradicted by study ABS-AS-201, in which effects of ProAir RespiClick were numerically equal to or greater than those of ProAir HFA.

Differences between effects of 90 mcg and 180 mcg ProAir RespiClick albuterol doses were not statistically significant.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

ProAir RespiClick is a multi-dose dry powder inhaler (MDPI) containing albuterol sulfate, a short-acting β_2-adrenergic receptor agonist, proposed for the treatment or prevention of bronchospasm with reversible obstructive airway disease in patients 12 years of age and older, and for the prevention of exercise induced bronchospasm in patients 12 years of age and older.

2.1.2 History of Drug Development

ProAir RespiClick (albuterol MDPI)for the treatment or prevention of bronchospasm with reversible obstructive airway disease, and the prevention of exercise induced bronchospasm, was introduced to the Agency under IND 104,532 on January 1, 2009.

In a pre-IND meeting on March 27, 2009, the Agency informed the applicant that, because the proposed albuterol MDPI is a novel formulation in a novel device, evaluation of efficacy and safety would entail a full clinical development program, including a dose-ranging study comparing efficacy and safety to a comparator product, a cumulative dose pharmacodynamic efficacy and safety study in patients with asthma and acute bronchospasm, and replicate 12-week randomized, placebo controlled chronic dosing efficacy and safety studies in patients with asthma.

At an end-of-phase-2 teleconference on August 30, 2010, the Agency stated that the phase 3 studies should be conducted in geographic regions with high humidity as well as in geographic regions with low humidity. In addition, the phase 3 studies would need to include a representative proportion of 12 to 16 year-old patients. The Agency also stated that, in the phase 3 studies, use of last observation carried forward (LOCF) to impute missing data would not be acceptable. The applicant proposed a repeated measures model instead of LOCF, using the 12-week average outcome. The Agency responded that, while a repeated measures model would be preferable to LOCF, the applicant should compare the first and last dose for efficacy to assess potential tachyphylaxis.

The Agency further confirmed that a single study in exercise-induced-bronchospasm (EIB) would be adequate if the proposed studies support approval for an indication of reversible obstructive airway disease.

In a pre-NDA teleconference on November 19, 2013, the applicant confirmed that a mixed-model repeated-measures analysis would be conducted for the phase 3 studies to evaluate efficacy over the entire treatment period, i.e. the average of the estimates at which FEV_1 data was collected. The applicant further confirmed that a comparison of efficacy results from the first and last visits would be conducted, and proposed sensitivity analyses for the phase 3 studies based on multiple imputation of missing data. The Agency deferred comment on the multiple imputation and suggested the applicant submit a detailed proposal for further evaluation.

2.2 Data Sources

Data for all five trials was provided by the applicant and is currently located at:

\\cdesub1\evsprod\NDA205636\0000\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis quality were adequate in this submission. Information requests to the applicant resolved issues concerning programs and macros missing in the original submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The current submission includes five trials to evaluate the safety and efficacy of albuterol MDPI for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise induced bronchospasm (Table 1 and Table 2). ABS-AS-101 (study 101) is a phase 1 cumulative dose efficacy and safety trial, ABS-AS-201 (study 201) is a phase 2 dose-ranging trial, ABS-AS-301 (study 301) and ABS-AS-304 (study 304) are phase 3 efficacy and safety trials in patients with asthma, and ABS-AS-302 (study 302) is a phase 3 efficacy trial in patients with exercise induced bronchospasm (EIB). These trials were conducted in the United States.

Table 1. Phase 1 and Phase 2 Studies in Current Submission

Study	Design	Population	Endpoints
ABS-AS-101 (101) Phase 1 2/13/10 to 6/21/10	M90 H90 Cumulative dose 1440 mcg 90 mcg/actuation 1+1+2+4+8 actuations 30 minutes apart X-over 2 period 3 to 14 day washout DB DD	Persistent asthma 18 to 45 years old 50%≤FEV_1≤80% pr Stable ICS N=47 USA only	*Primary:* ΔFEV_1 *Secondary:* ΔFEV_1 $AUC_{0\text{-}6hr}$
ABS-AS-201 (201) Phase 2 2/24/10 to 6/1/10	M90 M180 H90 H180 P Xover 5 way 10 sequence 3 to 7 day washout DB DD	Persistent asthma ≥12 years old 50%≤FEV_1≤80% pr Stable ICS N=71 USA only	*Primary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ *Secondary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ % pred

Source: Reviewer

M90 albuterol MDPI 90 mcg/actuation, M180 albuterol MDPI 180 mcg administered as two 90 mcg actuations, H90 Pro-Air HFA albuterol 90 mcg/actuation, H180 Pro-Air HFA albuterol 180 mcg administered as two 90 mcg actuations, DB double blind, DD double dummy, ICS inhaled corticosteroids, pr predicted

Table 2. Phase 3 Studies in Current Submission

Study	Design	Population	Endpoints
ABS-AS-301 (301) Phase 3 2/3/12 to 11/5/13	M180 P Parallel arm DB P to W12	Persistent asthma ≥ 12 years old 50%≤FEV_1≤85% pr[1] Stable ICS N=157 1:1 N=159 1:1 USA only	*Primary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ 12W *Secondary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ D1 ΔFEV_1 $AUC_{0\text{-}6hr}$ W1 ΔFEV_1 $AUC_{0\text{-}6hr}$ W12
ABS-AS-302 (302) Phase 3 3/26/13 to 6/4/13	M180 P Xover 2 sequence 2 way USA only	EIB 12 to 50 years old N=38	*Primary:* Max post-exc fall FEV_1 *Secondary:* Max post-exc fall FEV_1< 10%
ABS-AS-304 (304) Phase 3 12/3/12 to 11/1/13	M180 P Parallel arm DB P to W12	Persistent asthma ≥ 12 years old 50%≤FEV_1≤85% pr[1] Stable ICS N=159 1:1 USA only	*Primary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ 12W *Secondary:* ΔFEV_1 $AUC_{0\text{-}6hr}$ D1 ΔFEV_1 $AUC_{0\text{-}6hr}$ W1 ΔFEV_1 $AUC_{0\text{-}6hr}$ W12

Source: Reviewer

1. 50%≤FEV_1≤85% predicted among patients 12 to 17 years old, and 50%≤FEV_1≤80% predicted among patients ≥18 years years old, EIB exercise induced bronchospasm

3.2.1.1 Study101

Cumulative dosing phase 1 study 101 (Table 1) randomized 47 adult patients with persistent asthma to a double-blinded, double-dummy sequence of M90/H90 or H90/M90. Each treatment within a sequence was administered during a single visit in five sets of 90 mcg actuations: 1+1+2+4+8 for total cumulative doses of 90, 180, 360, 720, and 1440 mcg respectively. For each treatment, actuations within sets were separated by 15 to 30 seconds, and actuations between sets were separated by 30 minutes. Serial FEV_1 assessments were conducted 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, and 6 hr following the final cumulative dose. A wash out period of three to fourteen days was enforced between each treatment.

Randomization to sequence was stratified by participation in a PK sub-study and conducted in blocks of four patients, with double-dummy placebo administered to maintain blinding.

At each study visit, the first baseline pre-dose FEV_1 value was measured between approximately 6:00 AM and 11:00 AM, within 1 hour of the time at which FEV_1 was measured during the screening visit. Pre-dose FEV_1 was measured 30 minutes and 0 minutes prior to treatment administration.

The primary objective was to compare the efficacy of albuterol MDPI to HFA after a cumulative dose of 1440 mcg of albuterol.

The primary efficacy endpoint was baseline-adjusted FEV_1 30 minutes after each of the five cumulative doses. The secondary efficacy endpoint was baseline adjusted FEV_1 $AUC_{0\text{-}6hr}$ following the final dose administration for each treatment.

The primary efficacy 'endpoint' for study 101 was not a single endpoint, but instead was five endpoints, i.e., FEV_1 after each of the five cumulative doses. Over those five endpoints, type 1 error was not controlled because there was no preplanned analysis hierarchy. Even if a single endpoint had been chosen as primary, as we shall see in Section 3.2.2.1 , the margin for the prespecified noninferiority analysis was also flawed. Therefore the results from study 101 will be used only to characterize descriptively the relationship between effects of albuterol HFA and MDPI.

3.2.1.2 Study201

The objective of study 201 (Table 1) was to evaluate the efficacy of M90, M180, H90, and H180 for the treatment or prevention of bronchospasm in patients 12 years of age and older with persistent asthma.

Study 201 evaluated M90, M180, H90, H180, and placebo in a five-way Williams crossover design,[1] randomizing 71 patients with persistent asthma to one of ten treatment sequences in two Latin square blocks of five sequences each. A complete Williams design was assigned for each study center. Within each sequence, the washout period between treatments was three to seven days.

To maintain blinding, patients received four actuations at each treatment administration, two from an MDPI and two from an HFA, with treatments M180 and H180 administered as two actuations of M90 and H90 respectively. The time between actuations was 15 to 30 seconds.

Each treatment visit included collection of spirometry data 30 and 5 minutes prior to dosing as well as 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, and 6 hours after dosing. At each of the five study visits, the first baseline FEV_1 value was measured between approximately 6:00 AM and 11:00 AM, within 1 hour of the time at which FEV_1 was measured during the screening visit.

The primary efficacy endpoint was FEV_1 $AUC_{0\text{-}6hr}$.

3.2.1.3 Study 302

Study 302 (Table 2) was a two-treatment, two-sequence, two-way crossover trial which randomized 38 patients 15 to 50 years of years of age and older with EIB to one of two dosing sequences M180/P or P/M180. Within each sequence, a dose was given once, approximately 30 minutes prior to an exercise challenge.

A minimum washout time of two days was maintained between periods.

[1] Williams crossover designs provide estimates of treatment differences which are not aliased with sequence or period effects, but which are aliased with carryover effects. The designs are balanced and uniform, i.e., equal numbers of patients receive each treatment within a period and the sequence for each patient includes every treatment.

At each treatment visit, FEV_1 was measured 30 and 5 minutes prior to administration of treatment, 30 minutes after treatment and five minutes prior to the exercise challenge, and 5, 10, 15, 30, 60 minutes after the exercise challenge. All predose measurements were conducted between 6:00 AM and 11:00 AM.

Blinding was maintained by use of double-dummy dispensers.

The primary efficacy endpoint was maximum percentage decline from pre-exercise baseline FEV_1 within 60 minutes after the exercise challenge. Pre-exercise baseline FEV_1 was defined as FEV_1 measured five minutes before the exercise challenge.

The secondary efficacy endpoint was percent of patients whose maximum percentage post-exercise decline from baseline FEV_1 was less than 10%.

3.2.1.4 Studies 301 and 304

Studies 301 and 304 (Table 2) were double-blind, double-dummy, parallel arm trials which randomized patients 12 years of age or older with persistent asthma, to M180 or P QID in a 1:1 ratio. Trial 301 randomized 158 patients, and trial 304 randomized 159 patients.

Planned treatment visits at days 1, 8, and 85, plus or minus a 2 day window, included collection of spirometry data 30 and 5 minutes prior to dosing as well as 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, and 6 hours after dosing.

Patients were instructed to withhold study medication, ICS, and rescue medications for at least six hours before treatment visits. The first pre-dose FEV_1 was obtained at each visit between 6:00 AM and 11:00 AM and within 1 hour of the FEV_1 measurement recorded at the patient screening visit.

Between treatment visits, patients continued on their assigned treatments.

The primary efficacy endpoint was FEV_1 $AUC_{0\text{-}6hr}$ over the 12 weeks of randomized treatment, using measurements taken at weeks 1, 2, and 12.

3.2.2 Statistical Methodologies

3.2.2.1 Study 101

The primary analyses compared albuterol MDPI to HFA for FEV_1 after each of the cumulative doses: 90, 180, 360, 720, and 1440 mcg. However, as stated in Section 3.2.2.1, control of type 1 error over those five primary endpoints was inadequate, with no prespecified testing hierarchy. Even if the study were modified to evaluate a single primary endpoint, the planned analysis could not be considered pivotal or confirmatory because the planned statistical comparison, non-inferiority of albuterol MDPI to HFA, was based on an incorrectly calculated non-inferiority margin. In particular, calculation of the non-inferiority margin was based on only a single historical study, IX-100-076, rather than on multiple historical studies. Additionally, the quantity of albuterol per actuation in that historical study differed from that in the proposed to-be-marketed product, with 100 mcg rather than 90 mcg administered per actuation. Also, the non-inferiority margin was calculated as 50% of the *mean* difference between albuterol MDPI and placebo rather than as 50% of the *lower 95% confidence limit* of that difference. Fourth, the applicant did not provide any evidence that the proposed non-inferiority margin, a 200 mL difference in FEV_1, is not clinically meaningful.

Because the proposed non-inferiority margin was calculated incorrectly, results from study 101 will be considered descriptive rather than confirmatory, based on means and 90% confidence intervals (standard for non-inferiority studies) for differences in efficacy between albuterol MDPI and HFA.

Missing spirometric values were imputed with baseline value among subjects who started but did not complete the 6-hour evaluation of serial FEV_1 measurements. Five patients did miss time points for serial spirometry; however each of them missed only a single timepoint.

As specified by the applicant, the primary statistical analysis was a mixed-effect analysis of variance (ANOVA) model with fixed effects for baseline FEV_1, sequence, treatment group, period, pooled center, cumulative dose, cumulative dose by treatment interaction, and random effect for patient within sequence, with an AR(1) or constant correlation matrix (whichever fits better) between times within patients.

The prespecified analysis population for the primary analysis to analyze was the per-protocol (PP) population rather than intent-to-treat population (ITT). To protect the randomization, analyses presented here will be based on the ITT population. Still, as in any non-inferiority design, use of the ITT rather than the PP population may actually favor approval of the product tested – in this study results from the PP population are similar to those from the ITT population and the difference will therefore not be further addressed.

As a final note on the planned primary analysis, the applicant planned to call albuterol MDPI and HFA 'equivalent' if non-inferiority was established. However, non-inferiority neither establishes equivalence nor does it establish that one treatment is not inferior to the other. Instead, non-inferiority implies that the diminishment of treatment effect in the experimental drug compared to the reference drug does not exceed a prespecified non-inferiority margin.

3.2.2.2 Study 201

In contrast to the title of this study, "A Double-Blind, Randomized, Placebo–Controlled, 5-Way Crossover, Multicenter, Single Dose, Dose-Ranging Study to Compare the Efficacy and Safety of Albuterol [MDPI] and ProAir HFA ..." no statistical tests were planned to compare different albuterol doses in a dose ranging design. Instead, planned statistical tests compared each active treatment group to placebo.

For the primary analysis, FEV_1 $AUC_{0\text{-}6hr}$ for each active treatment group was compared to placebo to using a mixed-effect ANOVA with fixed effects baseline, sequence, treatment group, period, and pooled center, and with random effect patient within sequence.

To control type 1 error, comparisons were conducted in the following ordered hierarchy: M180 vs P, M90 vs P, H180 vs P, and H90 vs P. Each test was conducted at the two sided 0.05 level of significance.

The primary efficacy analysis was conducted on the ITT population, consisting of all patients receiving at least one dose of assigned study medication and with at least one post-baseline assessment.

Missing spirometry data was not imputed.

3.2.2.3 Study 302

The primary endpoint was analyzed using a mixed-effect ANOVA with fixed effects for sequence, treatment group, period, and center, within period baseline FEV_1 as a covariate, with random effect patient within sequence, and with Kenward-Roger adjustment for degrees of freedom.

The planned analysis for the secondary endpoint was a mixed effect logistic regression model with fixed effects for sequence, treatment group, period, and pooled center, within period baseline FEV_1 as a covariate, and with random effect for patient within sequence.

Analyses were conducted at the 0.05 level of significance, on all randomized patients who received at least one dose of the study medication and had at least one post-baseline assessment.

3.2.2.4 Studies 301 and 304

Primary and secondary endpoints were evaluated using a mixed model repeated measures analysis with fixed effects for treatment, baseline on study day, pooled site, study day (1, 8, or 84), and study day by treatment interaction, random effect for patient, Kenward-Roger adjustment for degrees of freedom, and a compound symmetric covariance matrix. The baseline for each day was the average of the two predose measurements. Missing data was not imputed.

Analyses were conducted at the 0.05 level of significance on all randomized patients who received at least one dose of the study medication and at least one post-baseline assessment.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no obvious differences between treatment groups for demographic and baseline characteristics which would affect treatment outcome (Appendix A).

Patterns of patient disposition did not appear to favor or disfavor use of albuterol MDPI. Trial completion exceeded 90% of randomized patients in all five studies reviewed. Of 47 patients randomized in study 101, two did not complete the study, one from each treatment sequence. Of 72 patients randomized in study 201, four did not complete the study, one did not receive at least one dose of randomized medication, one in the H90 arm who withdrew consent, one in the H90 arm who was withdrawn by the applicant due to a visit date outside the protocol window, and one in the placebo arm was lost-to-follow-up. In study 302, all patients randomized completed the trial. Similarly high completion rates were seen in studies 301 and 304 (Table 3 and Table 4).

Table 3. Patient Disposition, Study 301

Patient disposition	Number (%) of patients	
	Placebo MDPI (N=79)	Albuterol MDPI (N=79)
Completed	74 (94)	77 (97)
Withdrawn	5 (6)	1 (1)
Consent withdrawn	3 (4)	0 (0)
Protocol violation	1 (1)	0 (0)
Other	1 (1)	1 (1)

Source: CSR Table 7, page 64

Table 4. Patient Disposition, Study 304

Patient disposition	Number (%) of patients	
	Placebo MDPI (N=85)	Albuterol MDPI (N=75)
Completed	77 (91)	69 (92)
Withdrawn	7 (8)	6 (8)
Adverse event	1 (1)	2 (3)
Consent withdrawn	2 (2)	2 (2)
Noncompliance	1 (1)	1 (1)
Inclusion criteria not met	1 (1)	0 (0)
Other	2 (2)	1 (1)

Source: CSR Table 10, page 73

3.2.4 Results and Conclusions

3.2.4.1 Study 101

For each of the cumulative doses, the preplanned mixed effect model provided mean improvements from baseline FEV_1 (ΔFEV_1) observed 30 minutes after dosing which were numerically lower for albuterol MDPI compared to HFA (Table 5). Numerical differences between MDPI and HFA for change from baseline FEV_1 at the different cumulative doses ranged from 36 mL to 66 mL, with none statistically different at the 0.05 of significance. The overall mean treatment difference across cumulative doses was 47 mL and did not differ from 0 at the 0.10 level of significance.

Table 5. ΔFEV_1 after Cumulative Dosing, Study 101

Cumulative Dose	ΔFEV_1 mL (N)		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: CSR Table 14 2 2 2 1, reviewer program main study 101.sas

Relative potency of albuterol MDPI compared to albuterol HFA, both the ITT and per-protocol populations, was 0.55, with 90% confidence limits from 0.28 to 1.04 (Table 6). For demonstration of bioequivalence, EMA guidelines specify that the confidence limits for relative potency should lie entirely with the limits 0.67 to 1.5[2].

Table 6. Relative Potency of Albuterol MDPI compared to Albuterol HFA, Study 101

Relative Potency	(90% CI)
0.55	(0.28, 1.05)

source: reviewer program main study 101.sas

[2] CHMP (2009). Guideline on the requirements for clinical documentation for Orally Inhaled Products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1). EMA: London.

Mean $AUC_{0\text{-}6hr}$ increase from baseline of FEV_1 (ΔFEV_1 $AUC_{0\text{-}6hr}$) after a cumulative dosing of 1440 mcg was significantly less for albuterol MDPI than for albuterol HFA (Table 7).

Table 7. ΔFEV_1 $AUC_{0\text{-}6hr}$ after Cumulative Dose of 1440 mcg, Study 101

$\Delta AUC_{0\text{-}6hr}$ liter-hours (N)		**Difference (90% CI)**
HFA	**MDPI**	**HFA - MDPI**
3.802 (46)	3.372 (46)	0.43 (0.074, 0.787)

source: CSR Table 14 2 3 2 1, reviewer program main study 101.sas

Results from the analyses provided in this review numerically agree with those from the applicant. However, there are important differences in interpretation. In particular, the applicant states that "equivalence between ProAir [HFA] and [Albuterol MDPI] is demonstrated at all cumulative doses," a conclusion which seems unwarranted given that: (i) a non-inferiority study, or indeed any statistical study, cannot possibly demonstrate 'equivalence' between two treatments, (ii) a nominally significant difference between albuterol MDPI and HFA was seen in ΔFEV_1 $AUC_{0\text{-}6hr}$ after a cumulative albuterol dose of 1440 mcg, and (iii) the lack of statistically significant differences between albuterol MDPI and HFA for ΔFEV_1 and relative potency may have been due to lack of adequate sample size rather than 'equivalence' of effects.

Numerically, the estimated difference between albuterol MDPI and HFA for change from baseline FEV_1 30 minutes after treatment is approximately 47 mL.

3.2.4.2 Study 201

All treatments with albuterol provided significant increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ relative to placebo, regardless of inhaler (Table 8).

Table 8. ΔFEV_1 $AUC_{0\text{-}6hr}$, Albuterol versus Placebo, Study 201

$\Delta AUC_{0\text{-}6hr}$ liter-hr (N)					**Difference (P-Value)**			
M180	**H180**	**M90**	**HFA90**	**P**	**M180-P**	**H90-P**	**H180-P**	**H90-P**
1.394 (68)	1.328 (68)	1.214 (68)	1.124 (70)	0.244 (69)	1.15 (<.0001)	0.970 (<.0001)	1.083 (<.0001)	0.88 (<.0001)

source: CSR Table 5, reviewer program main study 201.sas

Compared to the HFA inhaler, the MDPI inhaler was associated with numerically greater increases in ΔFEV_1 $AUC_{0\text{-}6hr}$ which were not statistically significant (Table 9). Compared to the 90 mcg dose, for both inhalers, the 180 mcg dose was associated with a numerically greater increase in ΔFEV_1 $AUC_{0\text{-}6hr}$ which was not statistically significant (Table 9).

Table 9. ΔFEV_1 $AUC_{0\text{-}6hr}$, Differences between Albuterol Treatments, Study 201

$\Delta AUC_{0\text{-}6hr}$ liter-hr (N)				**Difference (P-Value)**			
M180	**H180**	**M90**	**H90**	**M180-H180**	**M90-H90**	**M180-M90**	**H180-H90**
1.394 (68)	1.328 (68)	1.214 (68)	1.124 (70)	0.066 (0.627)	0.090 (0.509)	0.180 (0.188)	0.204 (0.136)

source: reviewer program main study 201.sas

Time to onset of action was similar in the MDPI and the HFA product. Five nominal minutes after dosing, regardless of dose, both products showed statistically significant improvements from baseline FEV_1 compared to placebo (Table 10). Differences between products and between doses were not statistically significant (Table 11). Using actual minutes after dosing as a covariate yielded similar results after four minutes (Table 12 and Table 13). Results provided in Table 10 were within four or five mL, but did not exactly match, those provided by the applicant in CSR Table 14.2.1.4.

Table 10. ΔFEV_1 Five Nominal Minutes Post-Dose, Albuterol versus Placebo, Study 201

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: reviewer program main study 201.sas

Table 11. ΔFEV_1 Five Nominal Minutes Post-Dose, Differences between Albuterol Treatments, Study 201

ΔFEV_1 mL (N)				**Difference (P-Value)**			
M180	**H180**	**M90**	**H90**	**M180-H180**	**M90-H90**	**M180-M90**	**H180-H90**
289 (68)	304 (68)	273 (68)	270 (70)	-15 (0.586)	3 (0.904)	17 (0.543)	35 (0.200)

source: reviewer program main study 201.sas

Table 12. ΔFEV_1 Four Actual Minutes Post-Dose, Albuterol versus Placebo, Study 201

Min	ΔFEV_1 mL (N)					Difference (P-Value)			
	M180	H180	M90	H90	P	M180-P	M90-P	H180-P	H90-P
4	248	236	208	232	22	226	186	214	210
	(14)	(13)	(13)	(12)	(15)	(0.0001)	(0.0033)	(0.0005)	(0.0008)
5	236	272	272	245	-31	267	303	303	276
	(20)	(17)	(19)	(22)	(18)	(<.0001)	(<.0001)	(<.0001)	(<.0001)
6	302	301	244	303	31	271	212	269	272
	(16)	(20)	(17)	(18)	(14)	(<.0001)	(0.0003)	(<.0001)	(<.0001)

source: reviewer program main study 201.sas

Table 13. ΔFEV_1 Four Actual Minutes Post-Dose, Differences between Albuterol Treatments, Study 201

Min	ΔFEV_1 mL (N)				Difference (P-Value)			
	M180	H180	M90	H90	M180-H180	M90-H90	M180-M90	H180-H90
4	248	236	208	232	12	-24	40	4
	(14)	(13)	(13)	(12)	(0.84)	(0.71)	(0.51)	(0.94)
5	236	272	272	245	-36	27	-36	26
	(20)	(17)	(19)	(22)	(0.49)	(0.59)	(0.47)	(0.61)
6	302	301	244	303	2	-59	59	-2
	(16)	(20)	(17)	(18)	(0.97)	(0.27)	(0.28)	(0.97)

source: reviewer program main study 201.sas

To summarize, in study 201 no significant differences in effectiveness were seen between inhalers or between doses within inhalers.

3.2.4.3 Studies 301 and 304

In studies 301 and 304, treatment with albuterol MDPI 180 mcg provided significant increases in mean ΔFEV_1 $AUC_{0\text{-}6hr}$ relative to placebo over 12 weeks (Table 14), and for each timepoint during those 12 weeks (Table 15). Differences between timepoints in each study are not statistically significant since the 95% confidence limits overlap (Table 15).

Table 14. ΔFEV_1 $AUC_{0\text{-}6hr}$, Over 12 Weeks, Studies 301 and 304

Study	$\Delta AUC_{0\text{-}6hr}$ liter-hr (N)		Difference (P-Value)
	M180	P	M180-P
301	1.107	0.28	0.827
	(78)	(79)	(<.0001)
304	1.300	0.384	0.917
	(75)	(84)	(<.0001)

source: CSR Study 301 Table 12, CSR Study 304 Table 15, reviewer program main study 301 304.sas

Table 15. ΔFEV_1 $AUC_{0\text{-}6hr}$, by Study Day, Albuterol MDPI versus Placebo, Studies 301 and 304

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

source: CSR Study 301 Table 13, CSR Study 304 Table 16, reviewer program main study 301 304.sas

Change from baseline FEV_1 peaked within two hours after study drug administration (Figure 1 and Figure 2 for week 12). Change from pre-dose baseline FEV_1 differed significantly between placebo and M180 from 5 minutes to 4 hours after administration of randomized treatment (Table 16).

Figure 1. Change from Baseline FEV_1. Week 12, Study 301

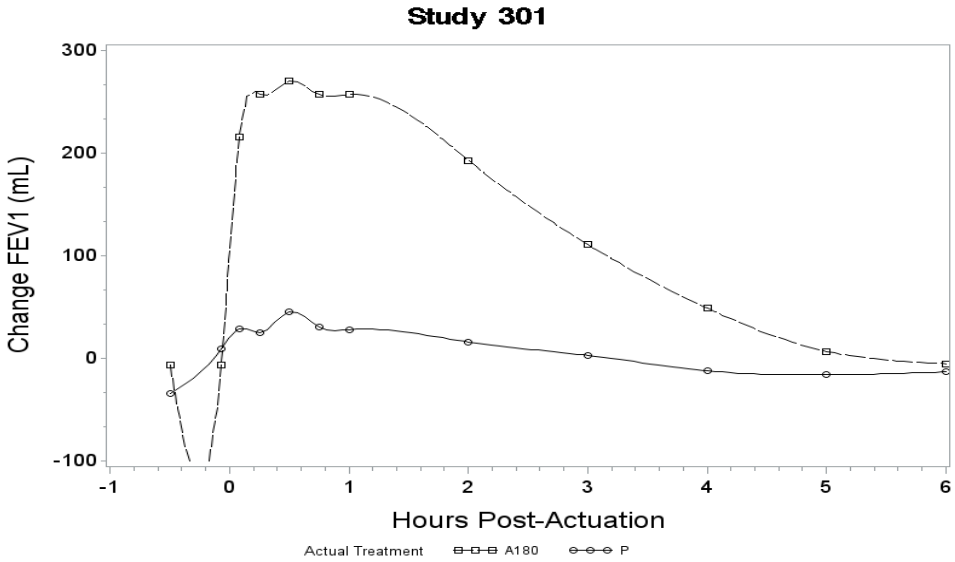
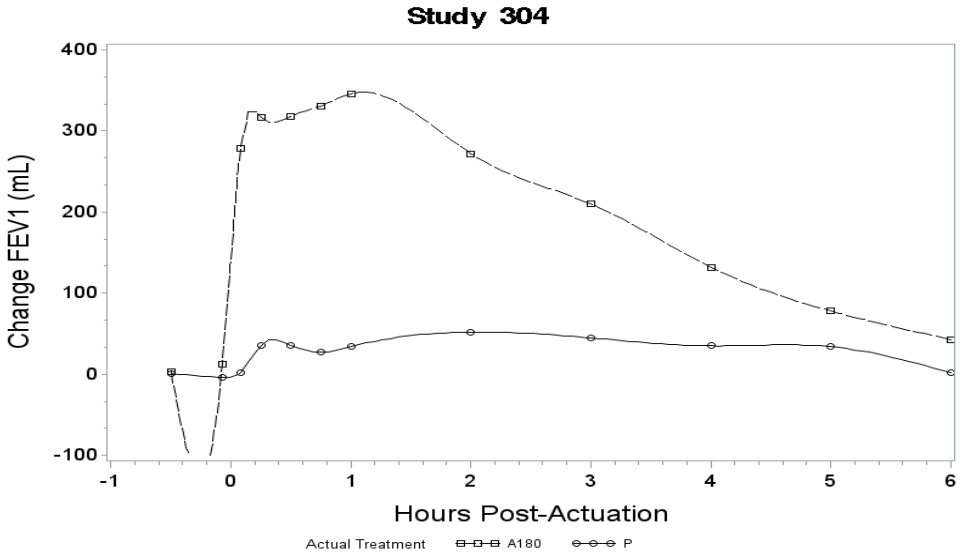


Figure 2. Change from Baseline FEV_1. Week 12, Study 304



source: CSR Study 301 Figure 15.2, CSR Study 304 Figure 15.2, reviewer program main study 301 304.sas

Table 16. ΔFEV_1 by Time after Treatment Administration, Week 12, Studies 301 and 304

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

source: reviewer program main study 301 304.sas

3.2.4.4 Study 302

Compared to placebo, treatment with M180 reduced maximum post-exercise decreases in FEV_1 (Table 17) and increased the percent of patients whose maximum post-exercise decrease in FEV_1 was less than 10% (Table 18).

Table 18 provides results from a simplified logistic analysis, with treatment as the only fixed effect, conducted by the applicant when the originally planned analysis failed to converge. However, for this review, the originally planned analysis, with all fixed effects, was successfully implemented using SAS proc GLIMMIX (rather than SAS proc NLMIXED employed by the applicant); the results of that analysis confirm those provided in Table 18.

Table 17. Maximum Exercise Induced Percent Decrease in FEV_1, Study 302

Max % Decrease FEV_1 (N)		**Difference (P-Value)**
M180	**P**	**M180-P**
6	22	-16
(38)	(38)	(<.0001)

source: CSR Table 11, reviewer program main study 302.sas

Table 18. Percentage of Patients with Maximum Exercise Induced Percent Decrease in FEV_1 <10%, Study 302

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

source: CSR Table 12, reviewer program main study 302.sas

3.3 Evaluation of Safety

Safety evaluations for this submission will be conducted by the Medical Reviewer, Keith Hull, M.D.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Differences in effectiveness according to gender, race, and age (study 302 <18 or ≥18 years of age; studies 301 and 304 <18, 18-64, or ≥65 years of age) were examined for each phase 3 study by adding each subgroup and subgroup by treatment interaction to the primary analysis with the treatment by subgroup interaction tested at the 0.05 level of significance. None of the subgroups tested had significant effects on treatment outcome.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

There is some evidence of quality control issues in the current submission. Calculations of relative potency in study 101 by the applicant appear to have incorrectly interchanged albuterol MDPI and Albuterol HFA. This is consistent with differences between Figures 3 and 14.5.11 in the applicant's clinical study report; the (b) (4) version appears numerically inferior to ProAir in Figure 3 but superior to ProAir in Figure 14.5.11 .

The quality control issues did not appear to critically impact results of regulatory interest in the submission.

5.2 Collective evidence

Despite the statistical issues identified during my review, the collective evidence clearly demonstrates efficacy of albuterol MDPI for the treatment and short-term prevention of reversible airway obstruction and for the prevention of exercise induced bronchospasm.

5.3 Conclusions and Recommendations

This submission demonstrates statistically significant benefits of ProAir RespiClick for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and the prevention of exercise induced bronchospasm. Studies 301 and 304 demonstrated that, compared to placebo, ProAir RespiClick improved FEV_1 $AUC_{0\text{-}6hr}$ and study 302 demonstrated that, compared to placebo, ProAir RespiClick provides a clear reduction in post-exercise bronchospasm.

There was little evidence that efficacy of ProAir RespiClick differed from ProAir HFA, a similar product. Study 101 provided weak evidence that the effect of ProAir RespiClick could be slightly less than comparable doses of ProAir HFA; however that result was contradicted by study 201, where effects of ProAir RespiClick were numerically equal to or greater than those of ProAir HFA.

Differences between effects of 90 mcg and 180 mcg albuterol were not statistically significant in the studies conducted.

5.4 Labeling Recommendations

The clinical studies section of the label should be reevaluated for potential: (b) (4)

(b) (4)

Appendix A: Demographic Characteristics

Table 19. Demographic Characteristics, Study 101

	Treatment Sequence	
	MDPI/HFA N=25	**HFA/MDPI N=22**
Age (years)		
Mean (SD)	31.3 (8.24)	35.5 (8.60)
Gender, n (%)		
Female	13 (52)	10 (45)
Male	12 (48)	12 (55)
Race, n (%)		
White	20 (80)	20 (91)
Black or African	5 (20)	2
Ethnicity, n (%)		
Hispanic or Latino	2 (8)	0
Not Hispanic or Latino	23 (92)	22 (100)

Source: CSR Table 12, page 77

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/s/

ROBERT ABUGOV
01/14/2015

DAVID M PETULLO
01/15/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205636 **Applicant: Teva** **Stamp Date: 5/5/2014**

Drug Name: Albuterol **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

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ROBERT ABUGOV
06/10/2014

DAVID M PETULLO
06/16/2014