CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205636Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDP BIOPHARMACEUTICS REVIEW

NDA#:	**205-636/S-000**
Submission Date:	5/5/2014
Drug Name:	Albuterol Sulfate Inhalation Powder (Albuterol Multi-Dose Dry Powder Inhaler)
Formulation:	Dry Powder Inhaler
Strength:	108 µg albuterol sulfate (90 µg albuterol base)
Applicant:	Teva Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA 505(b)(2)

BACKGROUND

Albuterol Multi-dose Dry Powder Inhaler (Albuterol MDPI) Inhalation Powder product contains a formulation of albuterol sulfate and lactose monohydrate, delivering 90 µg of albuterol base from the inhaler mouthpiece at each actuation.

RECOMMENDATION

ONDP-Biopharmaceutics has reviewed the NDA (b) (4) focusing on the two comparability protocols, which were found to be adequate from the biopharmaceutics perspective.

John Z. Duan -S
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John Duan, Ph.D. — 1/28/2015
Reviewer
ONDP Biopharmaceutics

Tapash K. Ghosh -S
Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2015.01.28 11:29:16 -05'00'

Tapash Ghosh, Ph.D. — 1/28/2015
Secondary Reviewer
ONDP Biopharmaceutics

cc: NDA 205-636 *DARRTS*

BIOPHARMACEUTICS EVALUATION

1. Introduction

Albuterol Multi-dose Dry Powder Inhaler (Albuterol MDPI) Inhalation Powder product contains a formulation of albuterol sulfate and lactose monohydrate, delivering 90 mcg of albuterol base from the inhaler mouthpiece at each actuation. It is proposed to be used for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

The clinical program consisted of 8 clinical studies: a cumulative dose Phase 1 study, a 5-way single-dose Phase 2 dose-ranging study and 5 Phase 3 studies that included 3 pivotal efficacy studies.

A Chemistry, Manufacturing and Controls (CMC) program has been implemented including a stability program on nine exhibit batches. Based on the testing at various orientations and conditions, as well as in- and out-of-package testing, the Applicant is proposing (b) (4) months expiry for the packaged product and 13 months expiry for the out-of-packag oduct.

There are two comparability protocols proposed: the first for a change in (b) (4) for one of the components; the other for an alternate site of manufacture of the device.

2. Product specifications

The product quality specifications include: Description, Appearance, Identification of the Drug Substances, Assay (Total Drug Content per Inhaler), Net Content (Fill) Weight, Related Substances by UPLC, Delivered Dose Uniformity (DDU), Aerodynamic Particle Size Distribution (APSD) by NGI, Water Content, Microbiological Examination for Non-Sterile Products, Number of Actuations per Inhaler, Residual Solvents and Foreign Particulates. Among them, the specifications for DDU and APSD are listed below.

For DDU:
The mean results of the beginning, middle and end are within (b) (4) % of label claim emitted dose.

The mean of the results combined from the beginning, middle and end (n=30 actuations) is within (b) (4) % of label claim emitted dose.

Tier 1 (n=10 inhalers):
NLT 27 out of 30 results are within (b) (4) % of label claim emitted dose.
All results are within (b) (4) % of label claim emitted dose.

Tier 2 (n=20 inhalers):

Determine the mean of 30 results from beginning the mean of the 30 results from the middle and the mean of the 30 results from the end and ensure all mean values are within (b) (4)% of label claim emitted dose.

NMT 9 of 90 determinations is outside (b) (4)% of the label claim emitted dose for 30 inhalers.

No result is outside (b) (4)% of the label claim emitted dose for 30 inhalers.

For APSD:
For n=5 inhalers perform determinations on each inhaler at beginning and end.

Report mass deposition in 4 groups:
Group 1 (MP/IP, Pre-Separator) (b) (4) µg
Group 2 (Stage 1, 2) (b) (4) µg
Group 3 (Stage 3, 4 & 5) (b) (4) µg
Group 4 (Stage 6,7 & MOC) (b) (4) µg

The mass balance is within (b) (4)% of label claim emitted dose for each individual test.

Note: *The APSD specifications were tightened for Group 1 from* (b) (4) *to* (b) (4) *µg, for Group 3 from* (b) (4) *to* (b) (4) *µg and for Group 4 from* (b) (4) *to* (b) (4) *µg.*

3. Comparability protocols

The two comparability protocols are summarized below.

A. (b) (4)

The Applicant has been notified that commercial supply of the existing (b) (4) is being discontinued. It is therefore proposed to replace the (b) (4) with an alternative (b) (4) The alternative material will be chosen to have similar characteristics and performance to the existing material.

The change to an alternative material grade has been risk assessed as low risk. The alternative material will undergo a (b) (4) qualification program. Albuterol MDPI devices will be manufactured using (b) (4) components made from the new (b) (4) These will undergo full batch release testing of sub-assemblies, they will be filled with drug formulation and will undergo full finished product release testing.

Upon prior agreement with FDA, the material change will be communicated to FDA through a CBE-30 Supplement with a comparability report based on original and new material batch release testing and finished product release testing.

The following is a summary of the proposed supportive information to be assembled prior to use of an alternate [redacted] and provided to FDA at time of submission:

- Alternate [redacted] details including supplier and material grade.
- Finished product release test results for the batch, including DDU and APSD results.

The acceptance criteria for the comparability studies will be:

- The sub-assemblies manufactured using the new material grade for the [redacted] meet the requirements for batch release tests as per QDP0060661 (see Section 3.2.P.7.3 for sub-assembly release specifications).
- The devices manufactured using the new materials meet the requirements for finished product release tests as per QDP0014951 (see Section 3.2.P.5.1 for finished product release specifications).

Should the predefined acceptance criteria not be achieved, a prior approval supplement shall be submitted providing supporting data justifying the change and rationale as to why the change will not adversely affect the efficacy or and safety of the final finished product.

Reviewer's Comments*: Due to the potential difference induced by the proposed material change, it is not certain that the product performance would be consistent before and after change. An in vitro bioequivalence using population approach (PBE) for DDU and APSD was considered to address this concern during the review. However, the product specifications include DDU and APSD as listed in Section 2 above. The product after change is subject to quality control and must meet the specification for DDU and APSD as listed in Section 2, which are considered to be sufficient.*

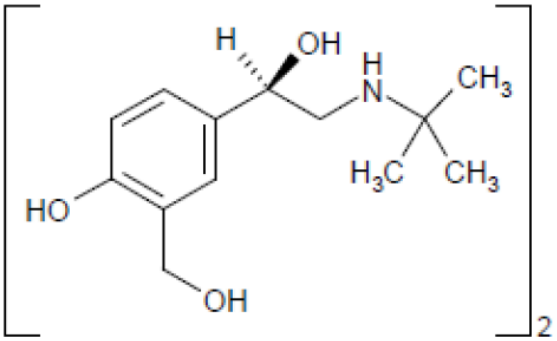
B. New Device Manufacturing Site

The exhibit and clinical batches of Albuterol MDPI used devices manufactured from sub-assemblies that had been [redacted] at [redacted] To meet the anticipated volume demands for Albuterol MDPI, a second manufacturing site for the device sub-assemblies is being developed at [redacted] This site will carry out comparable [redacted] test and release activities to those currently undertaken at the [redacted] site.

Upon prior agreement with FDA, the supply of commercial devices from the new site will be communicated to FDA through a CBE-30 supplement with a comparability report based on original and new manufacturing site batch release testing, finished product release testing and results from a minimum of six months stability testing. It is proposed that devices manufactured at the new site and subsequently filled with drug formulation will undergo finished product release testing and be placed on a stability program that will consist of:

- Three batches manufactured.
- Each batch will contain a different sub-assembly batch for each of the (b) (4) sub-assemblies (b) (4)
- Each batch will undergo full batch release testing of sub-assemblies (as per QDP0060719).
- Each batch will undergo full finished product release testing (as per QDP0014951). This includes functional and pharmaceutical performance testing including Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD) tests.
- Each batch will be placed on stability testing (Controlled Room Temperature (CRT) and Accelerated Conditions (ACC)) (as per QDP0014951). A minimum of 6 months stability test data will be provided.

Reviewer's Comments*: Due to the similar consideration as in the comparability protocol for* (b) (4) *material change, the proposed full finished product release testing is sufficient from the biopharmaceutics perspective.*

CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	205636 (Related NDA 21457, related IND 104532)
Submissions Date:	05/05/2014
Submission Type:	505(b)(2)
Proposed Brand Name:	ProAir RespiClick
Generic Name:	Albuterol Sulfate
Sponsor:	TEVA Pharmaceuticals
Route of Administration:	Inhalation
Dosage Form:	Multi-Dose Dry Powder Inhaler
Dosage Strength:	108 µg albuterol sulfate (equivalent to 90 µg albuterol) per actuation
Proposed Dosing Regimen:	• For prevention of bronchospasm, 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient. • For Prevention of exercise-induced bronchospasm, 2 inhalations 15 to 30 minutes before exercise
Proposed Indication(s):	• Treatment or prevention of bronchospasm with reversible obstructive airway disease • Prevention of exercise-induced bronchospasm
Proposed Population(s):	Patients 12 years of age and older
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Molecular Structure:	 H_2SO_4 and enantiomer

Note –

In this review, early development names Salbutamol MDPI, Albuterol (b) (4) and Albuterol MDPI sometimes were used to refer to the FDA-granted proprietary name ProAir RespiClick. Name of (b) (4) was denied by the Office of Prescription Drug Promotion according to proprietary name review by Dr. Lissa C. Owens from Division of Medication Error Prevention and Analysis.

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1. EXECUTIVE SUMMARY

TEVA Pharmaceuticals has submitted NDA 205636 under 505(b)(2) pathway seeking the marketing approval for albuterol sulfate Multi-Dose Dry Powder Inhaler (MDPI), for the indication of:

1) Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease;
2) Prevention of exercise-induced bronchospasm in patients 12 years of age and older.

The proposed dosing regimens are:

1) Treatment or prevention of bronchospasm in adults and adolescents age 12 and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.
2) Prevention of exercise-induced bronchospasm in adults and adolescents age 12 and over: 2 inhalations 15 to 30 minutes before exercise.

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

In this submission, Teva relied on its own approved product, NDA 021457 ProAir HFA, as a reference product for the purpose of PK, PD and efficacy comparisons in some of the Phase 1 and 2 trials. The dosing regimen of ProAir RespiClick is the same as ProAir HFA.

The major clinical pharmacology conclusions of this submission were summarized from the following pertinent clinical studies:

Study ABS-AS-101 was a Phase 1, multi-center, randomized, double-blind, double-dummy, cumulative-dose, two-period, crossover study in subjects with persistent asthma. Efficacy, PK and extra-pulmonary PD responses were compared following 1440 µg albuterol cumulative dose delivered via either ProAir RespiClick or ProAir HFA within 2 hours. The washout period between two periods was 3 to 14 days. The primary population included in the efficacy/PD and PK analysis was 39 and 16 patients, respectively.

Study ABS-AS-201 was a Phase 2, multicenter, randomized, double-blind, double-dummy, single-dose, 5-treatment, 10-sequence, placebo-controlled, crossover study comparing the bronchodilator response to ProAir RespiClick and ProAir HFA at two dose levels (90 µg and 180 µg) in subjects with persistent asthma. The washout period between treatments was 3 to 7 days. Total 71 subjects were randomized and treated with 68 completing the study.

Study ABS-AS-304 was a Phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of ProAir RespiClick relative to Placebo MDPI in subjects with persistent asthma. A subset of 15 patients from placebo MDPI group and16 patients from Albuterol MDPI group participated PK sub-study to evaluate the steady state PK.

The following points are the major findings of this review:

1) Albuterol systemic exposure was similar between ProAir RespiClick and ProAir HFA following cumulative dose (1440 µg in total) inhalation. The ratios (RespiClick/HFA) of AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively (Table 1.1 and Fig. 4.5).

2) Following 180 µg single dose inhalation, mean AUC_{0-t} and C_{max} of albuterol were 2147 (CV = 35.5%) pg*hr/mL and 325 (CV = 37.6%) pg/mL, respectively. The median T_{max} was approximately half an hour (range from ~10 minutes to ~5 hour). The steady state was reached following one week of QID dosing. The accumulation ratio of AUC_{0-6} was 1.7.

3) Some key efficacy PD responses were similar between ProAir RespiClick and ProAir HFA following 180 µg single dose inhalation. The percentage of responders (15% increase in FEV1 from baseline) was 63% and 52% for RespiClick and HFA, respectively. The median onset time for responders was 6 minutes for both products. The median times to peak FEV1 were 46.5 and 43.5 minutes for RespiClick and HFA, respectively. The mean durations of respond were 3.1 hour and 3.0 hour for RespiClick and HFA, respectively. These results were generally consistent with the approved label for NDA 021457 ProAir HFA.

4) The effects of albuterol on extra-pulmonary PD responses (i.e., systolic blood pressure, diastolic blood pressure, heart rate, QTc interval, and plasma glucose and potassium concentrations) were similar between ProAir RespiClick and ProAir HFA following cumulative dose inhalation. Although some differences were statistically significant, they were numerically small and are not considered to be clinically meaningful.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 205636 submitted on May 5, 2014 and has found the application approvable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Albuterol is a short-acting beta2-adrenergic receptor agonist used as a bronchodilator. Albuterol sulfate was first approved to treat asthma by FDA in 1981. Teva currently has three albuterol sulfate products approved: NDA21457 ProAir HFA® metered aerosol (approved in 2004), ANDA75343 albuterol inhalation solution (approved in 1999), and ANDA73419 albuterol oral syrup (approved in 1992).

Teva initiated an albuterol multi-dose dry powder inhaler (MDPI) program and a pre-IND meeting with FDA was held on 3/27/2009. The Division of Clinical Pharmacology commented that:

1) Blood samples should be collected for pharmacokinetic (PK) assessment in some of the studies to complete characterization of albuterol exposure of the proposed product (and the active comparator if there is one):

2) The bioequivalence (between the proposed product and the active comparator) was not the goal for PK studies.

On 1/27/2010, IND 104532 was safe to proceed. Liang Zhao, the clinical pharmacology reviewer, had no concerns regarding the study protocol (Protocol No. ABS-AS-101).

An End-of-Phase 2 meeting was held on 10/5/2010. The Division of Clinical Pharmacology commented that:

1) The Sponsor should consider obtaining first dose and steady state PK data at the proposed therapeutic dose in a subset of patients in one of the (Phase 3) studies for labeling purposes.

2) Based on Phase 1/2 safety, efficacy and PK results from adults, the Sponsor can initiate the pediatric Phase 1/2 PK studies without waiting for completion of the Phase 3 program in adults and adolescents.

A pre-NDA meeting was held on 11/19/2013 in which no specific clinical pharmacology-related question was raised.

To be noted, there were three versions of the albuterol MDPI device used in clinical studies:

1) (b) (4) was used for the first IVAX (b) (4) studies conducted outside the U.S. (IX-100-076 and IX-101-076; delivered 100 µg albuterol sulfate per actuation);

2) [redacted] was used in the supportive studies ABS-AS-101, ABS-AS-201, and ABS-AS-306;

3) [redacted] was used in the pivotal safety studies in asthma: ABS-AS-307, ABS-AS-301, and ABS-AS-304, and in the study in EIB, ABS-AS-302, and in study ABS-AS-308;

4) Two additional pediatric studies (ABS-AS-102 and ABS-AS-202) have been completed utilizing the [redacted] device and clinical study reports are in preparation.

It seems there is no difference in the mechanical dry powder delivery system between [redacted] and [redacted]. [redacted] has following modifications compared to [redacted] 1) [redacted] The inhalation devices are reviewed by Dr. Yong Hu from Office of New Drug Quality Assessment.

The efficacy and safety of the Phase 3 study ABS-AS-304 is reviewed by medical officer (Dr. Keith Hull) from DPARP.

1.3.2 PK Characteristics

Absorption:
Albuterol was rapidly absorbed into the systemic circulation following oral inhalation. The geometric mean AUC_{0-t} and C_{max} following 180 µg single dose inhalation were 2147 (CV = 35.5%) pg*hr/mL and 325 (CV = 37.6%) pg/mL, respectively (study ABS-AS-304). The median T_{max} was approximately half an hour (ranging from 10 minutes to 5 hour). Steady state was reached following QID dosing for 1 week. At steady state, the accumulation ratio was 1.67 and 1.48 for AUC_{0-t} and C_{max}, respectively (reviewer's analysis).

Distribution:
The volume of distribution of albuterol at steady state (V_{ss}) was estimated from 14 asthma patients in study ABS-AS-304. The geometric mean was 748 (CV = 44.0%) L (reviewer's analysis).

Metabolism:
Referring to the approved label of NDA 021457 ProAir HFA, the primary enzyme responsible for the metabolism of albuterol in humans is sulfotransferase (SULTIA3). The metabolism of (S)-albuterol is slower than (R)-albuterol as the exposure of (S)-albuterol is 3- to 4-fold higher than (R)-albuterol when albuterol was administered either intravenously or via inhalation after oral charcoal administration. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

Elimination:
Referring to the approved label of NDA 021457 ProAir HFA, the primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine. The effective half-life of albuterol delivered by ProAir RespiClick was approximately 5 hours.

1.3.3 Albuterol Systemic Exposure Comparison between ProAir RespiClick and ProAir HFA

For both ProAir RespiClick and ProAir HFA, albuterol is formulated for inhalation that exerts local effects in the lungs; the systemic bioavailability of albuterol is not a determinant of efficacy, but rather to address the safety concern due to its adrenergic activity. Bioequivalence is not the goal of cumulative dose study, but rather to provide the information of similarity of albuterol systemic exposure between two products to alleviate the safety concern.

Study ABS-AS-101 was a Phase 1, multi-center, randomized, double-blind, double-dummy, cumulative-dose, two-period, crossover study in subjects (18 to 45 years of age) with persistent asthma. Cumulative dose of 1440 µg albuterol (90, 180, 360, 720, and 1440 µg with 30 minutes as dosing interval) was administered via either ProAir RespiClick or ProAir HFA during each period. The washout period between two periods was 3 to 14 days. PK samples were collected at pre-dose, 15 minutes post-dosing following each of the five cumulative doses, and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours following the fifth (final) cumulative dose.

Following inhalation of 1440 µg cumulative dose of albuterol, the ratios (ProAir RespiClick/ProAir HFA, N=16) of least-squares geometric mean AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively (Table 1.1). The results indicated that the systemic exposures of albuterol were generally comparable between the two products.

Table 1.1 Comparison of PK Parameters between ProAir RespiClick and ProAir HFA Following Inhalation of Cumulative dose of 1440 µg Albuterol (N=16) in Study ABS-AS-101

Parameter	Albuterol [redacted] (b) (4) (T)	ProAir HFA (R)	Ratio (T/R)	90% CI lower limit	90% CI upper limit
AUC_{0-t} (ng·hr/mL)	23.2 (20.6%, 16)*	20.9 (20.6%, 16)*	1.11	1.04	1.19
C_{max} (ng/mL)	4.42 (25.9%, 16)*	3.30 (24.0%, 16)*	1.34	1.17	1.53
T_{max} (hr)	2.48 (2.33, 2.68)#	3.04 (2.37, 4.18)#	-	-	-

*** Geometric least square mean (CV%, N). Estimated geometric means and CIs derived from a log-linear mixed model with fixed effects for sequence, treatment (device), period, site, and random effect for subject.**

 # Median values (range)

(Source: adapted from CSR ABS-AS-101 page 94, Table 20)

1.3.4 Comparison of Albuterol Extra-Pulmonary PD Effects between ProAir RespiClick and ProAir HFA

The effect of albuterol on extra-pulmonary PD responses such as vital signs, QTc interval, plasma glucose and potassium concentrations were evaluated in the same cumulative study ABS-AS-101.

Generally the PD responses were similar between ProAir RespiClick and ProAir HFA at each of the 15-minute post-dose time points (Table 1.2). The maximum mean changes and the weighted mean changes from baseline after the final cumulative dose were also comparable between two products. There were some comparisons such as heart rate increased statistically significantly greater by ProAir RespiClick than ProAir HFA, but the differences were numerically small (4.57 and 2.44 bpm for maximum and weighted mean, respectively).

The differences on PD responses between Albuterol [redacted] (b) (4) and ProAir HFA were presented during mid-cycle meeting held on 10/8/2014. Medical reviewer Dr. Keith Hull considered the differences were generally small and not clinically meaningful.

Table 1.2 Comparison of PD Responses between ProAir RespiClick and ProAir HFA Following Inhalation of Cumulative dose of 1440 µg Albuterol (N=16) in Study ABS-AS-101

PD Parameter	Trend for Both Treatment	Differences (90% CIs) at 15 minutes after each cumulative dose (T-R)	Difference (90% CIs) of Maximum Mean Changes after final dose (T-R)	Difference (90% Cis) of Weighted Mean Changes after final dose (T-R)
QTcB and QTcF (msec)	overall increase	upper limit of the 90% CIs < 10	upper limit of the 90% CIs < 10	upper limit of the 90% CIs < 10
Plasma Glucose Concentration (mg/dL)	overall increase	< 3 (90% CIs included 0)	3.80 (0.04, 7.55)*	0.51 (-1.52, 2.53)
Plasma Potassium Concentration (mM)	overall decrease	< 0.1 (90% CIs included 0)	-0.08 (-0.19, 0.02)#	-0.03 (-0.12, 0.05)
Diastolic Blood Pressure (mmHg)	overall decrease	< 2 (90% CIs included 0) except at 1440 ug*	-2.51 (-4.41, -0.89)*#	0.25 (-0.98, 1.48)
Systolic Blood Pressure (mmHg)	overall increase	< 3 (90% CIs included 0) except at 1440 ug*	0.14 (-2.83, 3.12)	0.17 (-1.64, 1.99)
Heart Rate (bpm)	overall increase	< 2 (90% CIs included 0) except at 1440 ug*	4.57 (1.87, 7.27)*	2.44 (0.75, 4.12)*

*** 90% CI did not include 0, indicating the difference between treatments was statistically significant.**
 # Mean minimum changes from baseline
T: test product ProAir RespiClick, R: reference product ProAir HFA
(Source: reviewer's summary from Table 4.10 to Table 4.22)

1.3.5 Comparison of Efficacy PD Responses between ProAir RespiClick and ProAir HFA

ProAir HFA was not included as a positive control in the pivotal Phase 3 studies for this NDA submission. Therefore, the comparison of efficacy PD endpoints between ProAir RespiClick and ProAir HFA in Phase 2 trials becomes noteworthy to evaluate the efficacy/safety differences between the 2 products.

Study ABS-AS-201 was a Phase 2, multicenter, randomized, double-blind, double-dummy, single-dose, 5-treatment, 10-sequence, placebo-controlled, crossover comparison of the bronchodilator response to ProAir RespiClick and ProAir HFA in subjects (ages 12 and older) with persistent asthma. The washout period between treatments was 3 to 7 days. Total 71 subjects were randomized and treated with 68 completed the study. Post-dose FEV1 were planned to be measured at 5, 15, 30, 45 minutes, then at 1, 2, 3, 4, 5, and 6 hours. However, when time-related endpoints were evaluated, the actual time points of each FEV1 recording, but not the planned time points were utilized.

The four single-dose active treatments were:

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

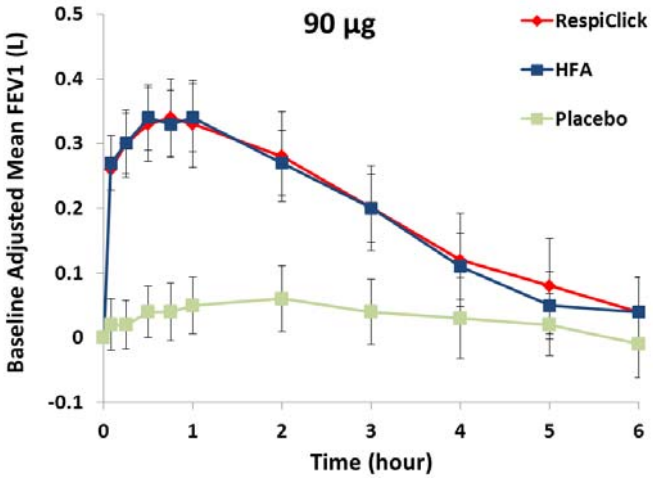
The primary efficacy endpoint was the baseline-adjusted area-under-the effect curve for FEV1 observed up to 6 hours following completion of dosing (FEV1 $AUEC_{0-6}$). Three following pertinent time-related endpoints were also evaluated:

- The time to response onset, defined as the first time that an increase from baseline in FEV1 of at least 15% from baseline within 30 minutes post-dose
- The time to maximum FEV1 post-dose
- The duration of effect (offset), defined as time from onset of a 15% or greater increase in FEV1 to offset of the 15% increase in FEV1 from baseline

The estimated mean baseline-adjusted FEV1 $AUEC_{0-6}$ for each of the four active treatments was significantly greater than that of placebo ($p<0.0001$) (Table 4.25). The baseline-adjusted peak FEV1 for each of the four active treatments increased at least 0.23 L greater than the placebo, indicating a significant bronchodilation effect for both products (Table 4.31). Although study ABS-AS-201 was not powered to detect the differences between four active treatments, FEV1 $AUEC_{0-6}$ comparison was explored between ProAir RespiClick and ProAir HFA at both doses (Fig.1.1).

FEV1 $AUEC_{0-6}$ was not significantly different between two products at both dose levels. Following 90 µg single dose inhalation, the difference (T-R) was 0.09 (95% CI = -0.13, 0.32) L·hr. Following 180 µg single dose inhalation, the difference (T-R) was 0.07 (95% CI = -0.16, 0.29) L·hr (Table 4.26).

A



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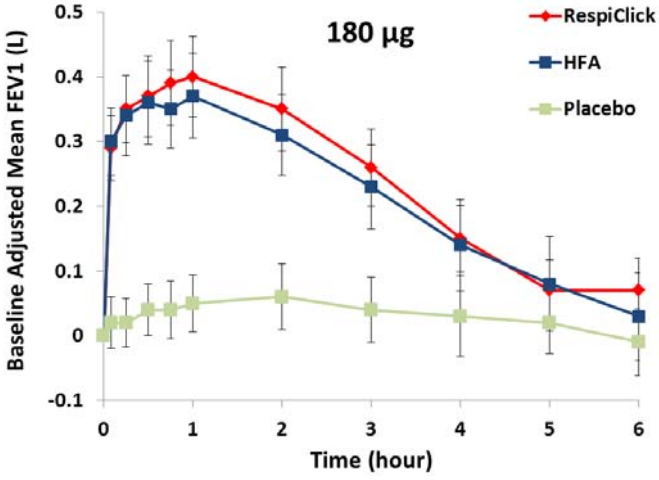

Fig.1.1 Arithmetic baseline-adjusted mean FEV1 following (A) 90µg albuterol, and (B) 180µg albuterol, single-dose inhalation in study ABS-AS-201. The red color represents ProAir RespiClick; the blue color represents ProAir HFA; the green color represents placebo. Error bars represent the 95% CI. (Source: adapted from CSR ABS-AS-102 page 62, Figure 1)

The percentage of responders (subjects achieving at least a 15% increase in FEV1 from baseline) was numerically comparable between ProAir RespiClick and ProAir HFA at both 90 µg and 180 µg dosing levels (Table 1.3). The median time to onset (15% or greater increase in FEV1 from baseline) was 6 minutes for all four active treatments. The median time to peak FEV1 was similar between four treatments, ranging from 43.5 minutes to 46.5 minutes. The mean duration of response (period between onset and offset of a 15% or greater increase in FEV1) was similar between four treatments, ranging from 2.8 hours to 3.2 hours.

Table 1.3 Comparison of Time-related Endpoints between ProAir RespiClick and ProAir HFA Following Inhalation of single dose Albuterol (N=71) in Study ABS-AS-201

Treatment		Responder N (%)[1]	Time to Response (min)[2]	Time to Peak FEV1 (min)[2]	Duration of Response (hour)[3]
90 µg	RespiClick	30 (44.1%)	6 (3, 30)	44.5 (4, 356)	3.2 (1.75)
	HFA	36 (51.4%)	6 (3, 30)	44.5 (3, 299)	2.8 (1.69)
180 µg	RespiClick	43 (63.2%)	6 (3, 30)	46.5 (15, 361)	3.1 (1.71)
	HFA	35 (51.5%)	6 (3, 30)	43.5 (3, 238)	3.0 (1.59)
Placebo		2 (2.9%)	15 (4, 26)	64 (3, 360)	2.5

[1] number of responders with at least 15% increase from baseline FEV1 within 30 min post-dose.
[2] median (range)
[3] mean (SD)
(Source: reviewer's summary from Table 4.33 to Table 4.39)

Reviewer's comments:
In order to fully evaluate the similarity between ProAir RespiClick and ProAir HFA, some key results from study ABS-AS-201 was compared with the approved label of NDA 021457 ProAir HFA in Table 1.4. The difference of time to response for ProAir HFA in 2 studies may be attributed to the inter-study variability. Since the mean value of the duration of response is not available in the label, the median values were compared. The duration was numerically longer following ProAir RespiClick inhalation.

Table 1.4 Comparison of Some Key Parameters from Study ABS-AS-201 with ProAir HFA Approved Label

	NDA 021457 ProAir HFA label[†#]	NDA205636	
		ProAir HFA[†]	ProAir RespiClick[†]
Responder %	53.4%	51.5%	63.2%
Time to response (min)*	8.2	6	6
Time to Peak FEV1 (min)*	47	43.5	46.5
Duration (hour)*	~ 3	2.9	3.8

† Results from 180 µg albuterol single/first dose
 # Results following first dose inhalation from a 6-week, randomized, double-blind, placebo-controlled study in 58 adult and adolescent patients of asthma
*** Median time**
(Source: reviewer's analysis)

2. QUESTION BASED REVIEW

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

Table 2.1 List of Five Clinical Pharmacology Studies in NDA205636 Submission Package

Study ID	Phase	Subjects	Dosing Regimen**	Comparator	Objectives
ABS-AS-101	1	45 asthma adults completed	cumulative dose of 1440 ug (cumulative 1, 2, 4, 8, 16 inhalations, each dose 30 min apart)	ProAir HFA (90 µg/act), Placebo	PK/PD, efficacy, safety
ABS-AS-201	2	68 asthma adults and adolescents completed	single dose (90 r 180 µg)	ProAir HFA (90 µg/act), Placebo	Efficacy/PD, safety
ABS-AS-304	3	146 asthma adults and adolescents	180 µg QID, 12-week	Placebo	PK, efficacy, safety
IX-100·076*	2	59 asthma adults completed	cumulative dose of 800 µg (cumulative 1, 2, 4, 8 inhalations, each dose 30 min apart)	Ventolin MDI (100 µg/act), Ventolin Diskhale (200 µg/act), Ventolin Accuhaler (200 µg/act), Placebo	Efficacy/PD, safety
ABS-AS-102 (summary)	1	15 children (4 to 11 years) completed	180 µg single-dose	ProAir HFA (100 µg/act)	PK/PD, safety

*** Study was conducted in South Africa by using early MDPI device (b) (4) with the by-then product name as albutamol-MDPI.**
**** Dose is defined as albuterol base does.**

2.2 General Attributes of the Drug

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

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

Table 2.2 outlines the quantities of each active ingredient and excipient per container. Each container has a minimum of 200 doses. Under the test conditions (airflow rate, Q, that produces a pressure drop of 4 KPa over the inhaler to be tested and at a duration consistent with the withdrawal of 2 L of air from the mouthpiece of the inhaler), each actuation delivers 108 µg albuterol sulfate (equivalent to 90 µg albuterol) with (b) (4) mg lactose monohydrate (b) (4)

Table 2.2 Ingredients and Their Quantities per Albuterol MDPI Inhaler Container

Ingredients	Quantity
Albuterol sulfate	(b) (4) mg
Lactose monohydrate	(b) (4) g
Target fill weight per device	0.65 g
Fraction of drug substance (%w/w)	(b) (4) %

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

Beta2-adrenergic receptor is a (b) (4) receptor (b) (4) activation of adenylcyclase and to an increase in the intracellular concentration of cAMP. This increase of cAMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol is a selective beta2-adrenergic receptor agonist (b) (4)

The proposed therapeutic indications of ProAir RespiClick are:

- 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.

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

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

- Treatment or prevention of bronchospasm in adults and adolescents age 12 and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.
- Prevention of exercise-induced bronchospasm in adults and adolescents age 12 and over: 2 inhalations 15 to 30 minutes before exercise.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

Currently there are 4 selective short-acting beta2-adrenergic receptor agonists approved in the U.S. indicated for bronchospasm:

- Albuterol HFA (such as NDA21457 ProAir HFA, NDA20983 Ventolin HFA, and NDA20503 Proventil HFA), albuterol inhalation solution (such as ANDA74543, ANDA74880, ANDA75050, and ANDA 075063), or albuterol syrup/tablet (such as ANDA73419, ANDA74454, and ANDA74749).
- Levalbuterol [(R)-enantiomer of albuterol] HFA (NDA21730 Xopenex HFA) and levalbuerol inhalation solution (such as NDA20837 Xopenex).
- Metaproterenol inhalation solution (such as ANDA70804, ANDA71786 and ANDA 75586), metaproterenol tablet (such as ANDA72024 and ANDA72025).
- Pirbuterol metered dose inhaler (MDI, NDA020014).

However, if approved, NDA205636 ProAir will be the first dry powder inhaler for albuterol.

2.3 General Clinical Pharmacology

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

Primary endpoints such as peak FEV1 (study IX-100-076), FEV1 at post-dose 30 minutes (study ABS-AS-101), FEV1 AUC_{0-t} (ABS-AS-201 and ABS-AS-3-4) were spirometry endpoints directly measuring the pulmonary ventilation function. All these endpoints were measured by spirometer.

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

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

(b) (4)

(b) (4)"In general, levalbuterol HFA produced (efficacy) results similar to racemic albuterol HFA." However, the safety profile of Levalbuterol was not significantly better than the racemic albuterol according to the same review (page 8): "In adults, asthma-related adverse events tended to be more common in the active treatment groups than placebo, with a slightly higher incidence in the levalbuterol HFA treatment group than in the racemic albuterol HFA group." Therefore it seems that (b) (4) (R) - enantiomer of albuterol has no significantly greater benefit/risk ratios than 90 µg racemic albuterol.

2.4 Exposure response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Due to its local action, the systemic exposure of albuterol is not an expected determinant of efficacy. No exposure-response relationship for efficacy was evaluated.

The cumulative dose-response relationship for efficacy was investigated in Phase 2 studies IX-100-076 (device (b) (4) and ABS-AS-101 (device (b) (4)). By visual check, it seems that the primary endpoint, 30 minutes post-dose FEV1 response, increases proportionally with the cumulative dose from 90 µg to 1440 µg (Fig. 4.3). However this cumulative dose-response cannot be translated into simple dose-response relationship as the real dose of albuterol accumulated in the lung over time is unknown.

Dose-response was explored at 2 dose levels (90 µg and 180 µg) in Phase 2 single-dose study ABS-AS-201. FEV1 $AUEC_{0-6}$ was not significantly different between two doses for both the proposed product (ProAir RespiClick) and the reference product (ProAir HFA). For ProAir RespiClick, the difference (180 µg - 90 µg) was 0.18 (95% CI = -0.09, 0.45) L·hr; for ProAir HFA, the difference (180 µg - 90 µg) was 0.20 (95% CI = -0.06, 0.47) L·hr (Table 4.27). To be noted, study ABS-AS-201 was not powered to study

the dose-response relationship, neither was the dose-response relationship predefined as the primary or secondary endpoints of this study.

2.4.2 What are the characteristics of the exposure-response relationship for safety?

It's known that beta adrenergic agonists can produce cardiovascular effects, hypokalemia and hyperglycemia, due to its pharmacological effect. The short-term exposure-response relationships of some safety pharmacodynamic (PD) endpoints were evaluated in study ABS-AS-101. The effect of albuterol was compared between the proposed product (ProAir RespiClick) and the reference product (ProAir HFA) (Table 1.2).

The response trend for each endpoint was the same for both ProAir RespiClick and ProAir HFA. Both products prolonged the mean QTc interval (Fig. 4.6 and 4.7); increased mean plasma glucose concentration (Fig. 4.8); reduced mean plasma potassium concentration (Fig. 4.9); slightly reduced mean diastolic blood pressure (Fig. 4.10); slightly increased mean systolic blood pressure (Fig. 4.11); and accelerated mean heart rate (Fig. 4.12). The differences between two products were not statistically significant for each of the 15-minute post-dose time points up to cumulative dose of 720 µg albuterol. At the cumulative dose of 1440 µg albuterol, the differences were statistically significant for vital signs (blood pressures and heart rate) with the directions in favor of ProAir HFA. During post-final-dose monitoring period (6 hours for vital sign and 4 hours for lab test), the differences of maximal mean changes (proposed-reference) for plasma glucose concentration, diastolic blood pressure and heart rate were statistically significant with values of 3.80 (0.04, 7.55) mg/dL, -2.51 (-4.41, -0.89) mmHg and 4.57 (1.87, 7.27) bpm, respectively. For the interests of safety, the directions were in favor of ProAir HFA. The weighted mean increase for heart rate from ProAir RespiClick during post-final-dose period was also statistically greater than ProAir HFA with value of 2.44 (0.75, 4.12) bpm. The PD results were presented in the mid-cycle meeting on 10/08/2014 and the PD differences between two products were generally considered numerically small and not clinically meaningful.

2.4.3 Does this drug prolong the QT or QTc interval?

Referring to 2.4.2, both the proposed product (ProAir RespiClick) and the reference product (ProAir HFA) prolonged the QTcB and QTcF interval from baseline (Fig. 4.6 and 4.7). The upper limit of the 90% CI of the difference (proposed-reference) was less than 10 msec at all the 15-minute post-dose time points. The 90% CI of the differences of maximum and weighted mean changes of QTcB and QTcF interval were less than 10 msec as well (Table 4.12).

In accordance with Clinical Pharmacology primary Review of NDA 21457 ProAir HFA (Dr. Shinja R. Kim, DARRTS date 10/24/2003, page 4): "In conclusion, this study showed that there were no significant differences between the three products (including reference product Proventil HFA and (b) (4) (b) (4) for PK or PD parameters (including QTc interval)."

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Referring to 2.4.1, the systemic exposure of albuterol is not an expected determinant of efficacy.

2.5 PK Characteristics of the Drug

2.5.1 What are the characteristics of drug absorption?

Results from study ABS-AS-304 showed that following oral inhalation of single-dose 180 µg albuterol via ProAir RespiClick in 16 asthma patients, the geometric mean C_{max}, AUC_{0-10}, and AUC_{0-inf} were 325 (CV = 38%) pg/mL, 1620 (CV = 39%) pg·hr/mL, and 2147 (CV = 36%) pg·hr/mL, respectively (Table 4.46). The median T_{max} was approximately 29 minutes post-dose (ranging from 11 minutes to 5 hours).

Steady state was reached following 7 days, QID administration of 180 µg albuterol via ProAir RespiClick, the geometric mean C_{max} and $AUC_{0-\tau}$ at steady state were 479 (CV = 29%) pg/mL and 2041 (CV = 35%) pg·hr/mL respectively (Table 4.46). The median T_{max} was approximately 26 minutes post-dose (ranging from 15 minutes to 2 hours). The geometric mean of accumulation ratio at steady state was 1.67 and 1.48 for AUC_{0-t} and C_{max}, respectively (reviewer's analysis).

2.5.2 What are the characteristics of drug distribution?

The volume of distribution of albuterol at steady state (V_{ss}) was estimated from 14 asthma patients. The geometric mean was 748 (CV = 44.0%) L. (reviewer's analysis)

2.5.3 What are the characteristics of drug metabolism?

No dedicated *in vivo* and *in vitro* metabolism study was conducted under NDA205636. Referring to the approved label of NDA 21457 ProAir HFA, "the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)- albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3."

2.5.4 What are the characteristics of drug elimination?

No mass balance study was conducted under NDA205636. Referring to the approved label of NDA 21457 ProAir HFA, "The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine."

The estimated geometric mean effective half-life was 4.8 (95%CI = 3.7, 6.4) hours from 15 asthma patients (reviewer's analysis).

2.5.5 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

No dedicated studies investigated dose-concentration relationship in this NDA submission. Although results from cumulative dose study ABS-AS-101 showed that 15 minutes post-dose concentration increased proportionally with the cumulative dose (Fig.2.1), the cumulative dose-concentration relationship cannot be translated into simple dose-concentration relationship as there lacked the sufficient time-concentration data to build a full PK model to evaluate the relationship between drug clearance and dose in this study.

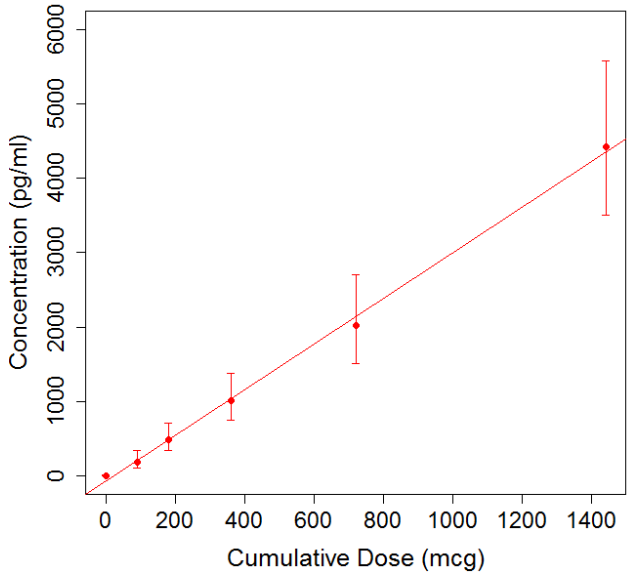

Fig.2.1 Geometric mean albuterol cumulative dose-concentration profiles of ProAir RespiClick in study ABS-AS-101 (N=16). PK samples were collected at pre-dose and 15 minutes after administration of each dose (90, 90, 180, 360, and 720µg with each dosing interval as 30 minutes). Error bars represent the standard deviation (concentration of BLQ was set at 1/2 of the value of LLOQ). The linear model represents the linear regression result (R square = 0.998). (Source: reviewer's analysis)

2.5.6 How do the PK parameters change with time following chronic dosing?

Results from study ABS-AS-304 showed that steady state was reached following 7 days, QID administration of 180 µg albuterol via ProAir RespiClick. Mean $AUC_{0-\tau}$ value (2041 pg·hr/mL) at steady state was comparable with AUC_{0-inf} value (2147 pg·hr/mL) from single-dose, which indicated the drug clearance remained the same following 7-day treatment. Geometric mean C_{max} and AUC_{0-6} at steady state were 1.47- and 1.67-fold as those from single-dose (Table 4.46). The median T_{max} (~26 minutes) was also comparable with that from single-dose (~29 minutes).

2.5.7 Is there evidence for a circadian rhythm of the PK?

The circadian rhythm of the PK was not evaluated in this NDA submission.

2.6 Intrinsic Factors

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

The above intrinsic factors on albuterol PK were not evaluated in this NDA submission.

2.6.2 Renal Impairment

The effect of renal impairment on albuterol PK was not evaluated in this NDA submission.

Referring to the approved label of NDA 21457 ProAir HFA, "The effect of renal impairment on the pharmacokinetics of albuterol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-

life, but there was a 67% decline in albuterol clearance. Caution should be used when administering high doses of ProAir HFA Inhalation Aerosol to patients with renal impairment."

2.6.3 Hepatic Impairment

The effect of hepatic impairment on albuterol PK was not evaluated in this NDA submission.

Referring to the approved label of NDA 21457 ProAir HFA, "The effect of hepatic impairment on the pharmacokinetics of ProAir HFA Inhalation Aerosol has not been evaluated."

2.6.4 Pediatric Patients

A significant number of adolescent (12 ≤ to < 18 years old) patients with persistent asthma or exercise-induced bronchoconstriction were consistently enrolled in all the Phase 3 studies (the ratio of adolescents: adults was 1:4 in pivotal studies 301 and 304). Although PK samples were not collected from adolescents [as reflected by Pre-IND and End-of-Phase 2 meeting minutes (DARRTS date 04/06/2009 and 10/15/2010, respectively), the Sponsor and the Agency did not specify that PK studies were necessarily to be conducted in adolescent patients], adolescent and adult patients were investigated as a single population for efficacy and safety evaluation in Phase 3 trials. The efficacy and safety of ProAir RespiClick in adolescent patients are reviewed by medical officer Dr. Keith Hull.

Pediatric PK profile was evaluated in 13 younger children (6 to 11 years) from single-dose study ABS-AS-102. Following administration of single dose (180 µg) albuterol via ProAir RespiClick, the geometric mean $AUC_{0\text{-}10}$, $AUC_{0\text{-}inf}$, and C_{max} for children were 1663 pg·hr/mL, 1953 pg·hr/mL and 353 pg/mL, respectively (Table 4.47). The results were comparable with the adults values obtained from study ABS-AS-304 (Table 4.48).

Systemic exposure was also compared between the proposed product (ProAir RespiClick) and the reference product (ProAir HFA) in study ABS-AS-102. The ratios (Albuterol MDPI/ProAir HFA) of $AUC_{0\text{-}t}$ and C_{max} were 1.056 (90% CI = 0.880, 1.268) and 1.340 (90% CI = 1.098, 1.636), respectively. The results were consistent with the adult ratios obtained from the cumulative dose study ABS-AS-101.

2.6.5 Geriatric Patients

In this NDA submission, clinical studies of ProAir RespiClick did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.
!
Referring to the approved label of NDA 21457 ProAir HFA, "No pharmacokinetic studies for ProAir HFA Inhalation Aerosol have been conducted in neonates or elderly subjects."

2.6.6 What pregnancy and lactation use information is available?

There were no adequate and well-controlled studies in pregnant women in this NDA submission.

Referring to the approved label of NDA 21457 ProAir HFA, "ProAir HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." (8.1)

"Because of the potential for beta-agonist interference with uterine contractility, use of ProAir HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk." (8.2)

"Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." (8.3)

2.6.7 Does genetic variation impact exposure and/or response?

The effect of genetic variation impact on albuterol PK was not evaluated in this NDA submission.

2.6.8 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Due to its local action, the systemic bioavailability of albuterol is not a determinant of efficacy. Referring to the approved label of NDA 21457 ProAir HFA, no dosage regimen adjustments are recommended.

2.7 Extrinsic Factors

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

The above extrinsic factors on albuterol PK were not evaluated in this NDA submission.

2.7.2 Drug-drug interactions (DDI)

2.7.2.1 Is the drug a substrate of CYP enzymes?

Referring to section 2.5.3, the (R)- albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3, but not CYP enzymes.

2.7.2.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The *in vitro/in vivo* CYP inhibitor/inducer studies were not conducted in this NDA submission.

2.7.2.3 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

The *in vitro/in vivo* P-gp studies were not conducted in this NDA submission.

2.7.2.4 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Referring to the approved label of NDA 21457 ProAir HFA, under section 7, DRUG INTERACTIONS,

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as ProAir HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable

alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics
The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin
Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

7.4 Monoamine Oxidase Inhibitors (MAOI) or Tricyclic Antidepressants
ProAir HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

2.7.2.5 Is there a known mechanistic basis for pharmacodynamics drug-drug interactions?

Referring to 2.7.2.4, the drug-drug interactions between albuterol and beta-blockers, diuretics and MAOIs are all pharmacodynamics-based.

2.8 General Biopharmaceutics

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

The Sponsor did not specify the biopharmaceutic class of albuterol. However, albuterol sulfate is (b) (4) soluble in water, (b) (4)

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

Although the albuterol sulfate formulation remained unchanged between Phase 1, 2 and 3, there were 3 versions of devices involved in this NDA submission:

1) Device (b) (4) was intended for marketing and used in Phase 3 trials ABS-AS-301, ABS-AS-302, ABS-AS-304, ABS-AS-307 and ABS-AS-308.

2) Device (b) (4) was used in Phase 1 trial ABS-AS-101, Phase 2 trial ABS-AS-201, and (b) (4)

3) Device (b) (4) was used during earlier development which the trials were conducted outside the U.S. (IX-100-076 and IX-101-076).

(b) (4)

2.8.3 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Establishing BE between ProAir RespiClick and ProAir HFA was not the goal of NDA 205636 as it involves different dosage forms and devices. In addition, systemic exposure is not a determinant of efficacy. A full clinical development program was conducted for NDA 205636.

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

The administration route of ProAir RespiClick is through inhalation. The effect of food on the bioavailability of albuterol was not studied in this NDA submission.

2.9 Analytical Section

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

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

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

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

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

The calibration curves in human plasma were constructed using eight non-zero standards at a concentration range of 2.00 pg/mL to 1000 pg/mL for Albuterol (Table 2.3). The lower limit of quantitation was 2.00 pg/ml. The coefficient of variation of precision and the relative error of accuracy were all within ±15% of the nominal value. There was no obvious interference from the blank matrix or among the analyte and internal standard. The results show that this method has sufficient specificity and selectivity. Albuterol was stable in human plasma when kept at approximately 4 °C for 18 hours. Albuterol in human plasma was stable when subjected to three freeze/thaw cycles at approximately -70 °C.

Table 2.3 Partial Method Validation Data Summary for Albuterol in Human Plasma

Calibration Curve Linearity				
Calibration Curve Range		2.00 pg/mL to 1000 pg/mL		
Lower Limit of Quantitation		2.00 pg/mL		
Calibration Curve		n = 1		
Slope		0.0080		
Intercept		0.0010		
Coefficient of Determination (R^2)		0.9979		
Precision & Accuracy				
	QC	**Conc. (pg/mL)**	**%CV**	**%RE**
Intra-Batch (n = 6)	Low	6.00	4.44	-5.00
	Middle	400	2.16	-5.75
	High	800	2.84	-1.25
Sensitivity				
Intra-Batch (n=6)	LLOQ	2.00	7.84	4.00
Extraction Recovery			**QCL/QCSL (%)**	**QCH/QCSH (%)**
		Albuterol	69.90	64.58
		Internal Standard	66.43	62.14
Matrix Effect			**QCSL/QCNL (%)**	**QCSH/QCNH (%)**
		Albuterol	131.41	117.49
		Internal Standard	129.43	114.56
Stability		**Conditions**	**%RE**	
			QCL	**QCH**
Matrix Freeze/Thaw Stability		3 Cycles at ~ -70 °C	-6.33	-5.88
Matrix Bench-Top Stability		~18 Hours at ~4 °C	-4.33	-5.50
Long-Term Stability		100 Days at ~ -20 °C	3.00	2.88
Long-Term Stability		100 Days at ~ -70 °C	2.67	2.63
Long-Term Stability		279 Days at ~ -70 °C	10.0	4.00
			%Diff.	
Stock Solution Stability		94 Days at ~ -20 °C	-1.62	
Extracted Sample Storage Reproducibility		**Conditions**	**%RE**	
			QCL	**QCM**	**QCH**
		3 Days at Ambient Temperature	-8.33	-7.25	-3.75
		3 Days at ~4 °C	-5.50	-4.25	-0.13
Dilution Integrity		**Conc. (pg/mL)**	**%RE**		
5-Fold Dilution (QCD5×)		1600	5.00		

2.10 Reference

1. Busse WW. Asthma and Rhinitis. 1995 (2) Part 20; p1545.
2. Henderson WR Jr, Banerjee ER, Chi EY. Differential effects of (S)- and (R)-enantiomers of albuterol in a mouse asthma model. J Allergy Clin Immunol. 2005 Aug;116(2):332-40.

3 DETAILED LABELING RECOMMENDATIONS

12.1 Mechanism of Action

Albuterol sulfate is a beta2-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta2-adrenergic receptors on airway smooth muscle. Activation of beta2-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta2-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta2-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes [*see Warnings and Precautions (5.4)*].

12.2 Pharmacodynamics

In a pharmacodynamic (PD) trial conducted in 47 patients, the PD and safety profiles were similar for TRADENAME and ProAir HFA. Comparable time-profile changes from baseline in the PD measures (serum (b) (4) glucose and, potassium concentrations, QTcB, QTcF, heart rate, systolic blood pressure, and diastolic blood pressure) were observed following cumulative dose administration up to 1440 mcg of both TRADENAME and ProAir HFA. The overall safety, efficacy and PD profile of TRADENAME and ProAir HFA were comparable.

In a single-dose Phase 2 study ~~also with~~~~assessing~~ PD assessment, 71 patients using TRADENAME had bronchodilator efficacy that was significantly greater than placebo and comparable to that of ProAir HFA at administered doses of 90 and 180 mcg in (b) (4) adolescent and adult subjects with persistent asthma. (b) (4)

(b) (4)

Cardiac Electrophysiology

As with other beta2-adrenergic agonists, TRADENAME [(b) (4)] prolonged QT intervals following a 1440 mcg cumulative dose. [(b) (4)] The prolong [(b) (4)] comparable to that of ProAir HFA.

12.3 Pharmacokinetics

[(b) (4)]

[(b) (4)]

[(b) (4)]

Absorption

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

[(b) (4)]

Distribution

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

Elimination

[(b) (4)]

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

Metabolism

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

Excretion

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

Specific Populations

Age: No pharmacokinetic studies for TRADENAME have been conducted in neonates or elderly subjects.

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

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

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

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

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

4. Appendix

4.1 Appendix – Individual Study Review

Note –
For reviews of individual studies, early development names Salbutamol-MDPI and Albuterol (b) (4) sometimes are used to refer to the FDA-granted proprietary name ProAir RespiClick.

4.1.1 Study IX-100-076

Study Type: Phase 2 efficacy/PD cumulative dose study in asthma adults

Title:
A Placebo-Controlled, Cumulative Dose-Response Study to Evaluate the Therapeutic Equivalence of a New Breath-Operated, Multi-Dose, Dry Powder Salbutamol Inhaler, Ventolin- Metered-Dose Inhaler, Ventolin Accuhaler and Ventolin Diskhaler

Objective:
The primary objective of this study was to evaluate the therapeutic equivalence of Salbutamol-MDPI and Ventolin-MDI.

The secondary objectives were:

- to establish that Salbutamol-MDPI was an effective treatment compared to placebo;
- to evaluate the therapeutic equivalence of Salbutamol-MDPI and Ventolin Diskhaler;
- to evaluate the therapeutic equivalence of Salbutamol-MDPI and Ventolin Accuhaler.

Study Design and Method:
This investigation was a randomized, evaluator-blind, dose-ranging, five-treatment, five-period, cross-over investigation. Following screening assessments, patients attended for five treatment periods with 4-7 days washout period between each treatment. Each treatment was a dose-ascending, cumulative fashion (four doses per treatment with dosing interval of 30 minutes). 80 patients were enrolled in the study and 65 were randomized to treatment. 61 patients were included in the per-protocol population. No PK samples were collected. The study was conducted in South Africa.

Some noteworthy inclusion criteria:

- Asthma (FEV1 of between· 50% and 80% predicted for age, height and gender) that had been stable for at least four weeks prior to screening as defined by clinical history
- Reversible bronchoconstriction as verified by a ~ 15% increase in FEV, within 30 minutes following inhalation of salbutamol 200 mcg (two 100 mcg actuations) from a Salamol®-MDI
- Patients receiving the following drugs prior to screening were not to use these medications during the study and should have been withdrawn from them for the period stated prior to screening:
  • Oral theophyl1ines (1 week)
  • Orall3,-agonists (1 month)
  • Long-acting inhaled l3,-agonists (1 month)
  • Antihistamines (1 month)
  • Inhaled and oral anticholinergics (1 month)
  • Inhaled and intranasal corticosteroids (1 month)

The dosing regimens of different treatments were:

- Test product (Salbutamol-MDPI): cumulative dose of 800 µg albuterol (1, 2, 4, 8 inhalations with 100 µg each actuation and dosing interval was 30 minutes).
- Ventolin-MDI: cumulative dose of 800 µg albuterol (1, 2, 4, 8 inhalations with 100 µg each actuation, the dosing interval was 30 minutes).
- Ventolin Diskhaler: cumulative dose of 1600 µg albuterol (1, 2, 4, 8 inhalations with 200 µg each actuation, the dosing interval was 30 minutes).
- Ventolin Accuhaler: cumulative dose of 1600 µg albuterol (1, 2, 4, 8 inhalations with 200 µg each actuation, the dosing interval was 30 minutes).
- Placebo-MDPI: dry powder inhaler containing lactose only (1, 2, 4, 8 inhalations with dosing interval of 30 minutes).

To be noted, the Salbutamol-MDPI device used in this study (b) (4) or IVAX (b) (4)) was different from the devices (b) (4) used in other studies that were submitted in this package.

Primary Endpoints:
The primary outcome variable for each treatment was to be the peak FEV1 at each dose level. The peak FEV1 response at each dose level was the maximum FEV1 determination observed between 0-30 minutes post-dose (FEV1 measured 2, 5, 10, 15 and 30 minutes post-dose) at each dose level.

Therapeutic equivalence at a given dose level would be declared if a 95% confidence interval for the treatment difference was contained within ± 20% of the FEV1 response for the reference products (Ventolin-MDI, Ventolin Diskhaler, Ventolin Accuhaler). Salbutamol-MDPI would be compared to placebo to establish that Salbutamol-MDPI was an effective treatment by the same methodology.

The secondary outcome efficacy variable was peak expiratory flow (PEF) at each dose of treatment. Therapeutic equivalence of the PEF dose response curves would be carried out using the same methodology described for FEV1.

Efficacy Measurement:
All spirometric evaluations (FEV1 and PEF) were made using a calibrated computerized spirometer with the patient in the sitting position and wearing a nose clip. Patients performed a minimum of three acceptable spirometric maneuvers within 30 minutes; the two highest FEV1 values had to be within 5% or 0.1 L (whichever was larger) of each other. The highest value was recorded for study-qualifying purposes.

Efficacy Results:
The mean baseline FEV1 calculated from average of 2 pre-dose values were similar between 5treatments, ranging from 2.47L to 2.54L (Table 4.1).

Table 4.1 Baseline FEV1 Characteristics by Treatment

Treatment	Subject N	Average of 2 Pre-dose FEV1 (L)*
Salbutamol MDPI	60	2.53 (0.67)
Ventolin MDI	57	2.47 (0.65)
Ventolin Diskhaler	56	2.51 (0.65)
Ventolin Accuhaler	58	2.52 (0.67)
Placebo MDPI	57	2.54 (0.69)

*** mean (SD)**
(Source: reviewer's summary based on CSR IX-100-076 page 68, Table 14.1.10)

FEV1 at screening for the per protocol population For the primary objective, ratios (Salbutamol/Ventolin) of the least square mean of peak FEV1 at the cumulative dose of 100 µg, 200 µg, 400 µg and 800 µg albuterol were: 1.02 (95% CI= 1.00, 1.04), 1.01 (95% CI= 0.99, 1.03), 1.00 (95% CI= 0.98, 1.02), and 1.00 (95% CI= 0.98, 1.02), respectively (Table 4.2).

Table 4.2 Comparison of Least Square Mean Peak FEV1 between Salbutamol-MDPI and Ventolin-MDI

Cumulative Dose (µg)	LS mean of Peak FEV1 (L)		Ratio (T/R)*	95% CI Lower Limit#	95% CI Upper Limit#
	Salbutamol - MDPI (T)*	Ventolin-MDI (R)*			
100	3.01	2.95	1.019	0.994	1.044
200	3.12	3.10	1.008	0.986	1.031
400	3.21	3.21	1.000	0.977	1.024
800	3.31	3.20	1.003	0.979	1.028

***T, test product; R, reference product**
 # 95% CIs, but not 90% CIs were pre-defined as boundary
(Source: reviewer's summary based on CSR IX-100-076 page 35)

For the secondary objective of comparison between Salbutamol-MDPI and Ventolin Diskhaler, ratios (Salbutamol/Ventolin) of the least square mean of peak FEV1 at the cumulative dose of 100/200 µg, 200/400 µg, 400/800 µg and 800/1600 µg albuterol were: 0.99 (95% CI= 0.96, 1.01), 0.98 (95% CI= 0.96, 1.01), 0.98 (95% CI= 0.96, 1.01), and 0.99 (95% CI= 0.97, 1.01), respectively (Table 4.3).

Table 4.3 Comparison of Least Square Mean Peak FEV1 between Salbutamol-MDPI and Ventolin Diskhaler

Salbutamol -MDPI (T)*		Ventolin Diskhaler (R)*		Ratio (T/R)*	95% CI Lower Limit#	95% CI Upper Limit#
Cumulative Dose (µg)	LS Mean Peak FEV1 (L)	Cumulative Dose (µg)	LS Mean Peak FEV1 (L)			
100	3.01	200	3.04	0.989	0.964	1.014
200	3.12	400	3.17	0.983	0.961	1.005
400	3.21	800	3.26	0.984	0.961	1.007
800	3.31	1600	3.35	0.990	0.965	1.014

***T, test product; R, reference product**
 # 95% CI, but not 90% CI was pre-defined
(Source: reviewer's summary based on CSR IX-100-076 page 39)

For the secondary objective of comparison between Salbutamol-MDPI and Ventolin Accuhaler, ratios (Salbutamol/Ventolin) of the least square mean of peak FEV1 at the cumulative dose of 100/200 µg, 200/400 µg, 400/800 µg and 800/1600 µg albuterol were: 1.02 (95% CI= 0.99, 1.04), 1.01 (95% CI= 0.99, 1.03), 1.00 (95% CI= 0.98, 1.03), and 1.00 (95% CI= 0.98, 1.03), respectively (Table 4.4).

For the secondary objective of comparison between Salbutamol-MDPI and placebo-MDPI, ratios (Salbutamol/placebo) of the least square mean of peak FEV1 at the cumulative dose of 100 µg, 200 µg, 400 µg and 800 µg albuterol were: 1.17 (95% CI= 1.14, 1.20), 1.21 (95% CI= 1.18, 1.24), 1.26 (95% CI= 1.23, 1.29), and 1.30 (95% CI= 1.27, 1.33), respectively (Table 4.5).

Table 4.4 Comparison of Least Square Mean Peak FEV1 between Salbutamol-MDPI and Ventolin Accuhaler

Salbutamol -MDPI (T)*		Ventolin Accuhaler (R)*		Ratio (T/R)*	95% CI Lower Limit#	95% CI Upper Limit#
Cumulative Dose (µg)	LS Mean Peak FEV1 (L)	Cumulative Dose (µg)	LS Mean Peak FEV1 (L)			
100	3.01	200	2.96	1.015	0.990	1.040
200	3.12	400	3.09	1.010	0.988	1.033
400	3.21	800	3.21	1.001	0.978	1.025
800	3.31	1600	3.31	1.002	0.978	1.027

***T, test product; R, reference product**
 # 95% CI, but not 90% CI was pre-defined
(Source: reviewer's summary based on CSR IX-100-076 page 39)

Table 4.5 Comparison of Least Square Mean Peak FEV1 between Salbutamol-MDPI and Placebo

Salbutamol -MDPI (T)*		Placebo-MDPI (R)*	Ratio (T/R)*	95% CI lower limit	95% CI upper limit
Cumulative Dose (µg)	LS Mean Peak FEV1 (L)	LS Mean Peak FEV1 (L)			
100	3.01	2.57	1.167	1.138	1.196
200	3.12	2.58	1.211	1.184	1.238
400	3.21	2.54	1.264	1.234	1.294
800	3.31	2.55	1.300	1.267	1.333

***T, test product; R, reference product**
 # 95% CI, but not 90% CI was pre-defined
(Source: reviewer's summary based on CSR IX-100-076 page 41)

The cumulative dose-response curves were similar for Salbutamol-MDPI, Ventolin-MDI, Ventolin-Diskhaler, and Ventolin Accuhaler (Fig.4.1). By visual check, they all achieved maximal effect following cumulative of 2 dosing units. The dose-response curve of placebo seems remained at pre-dose level without significant change.

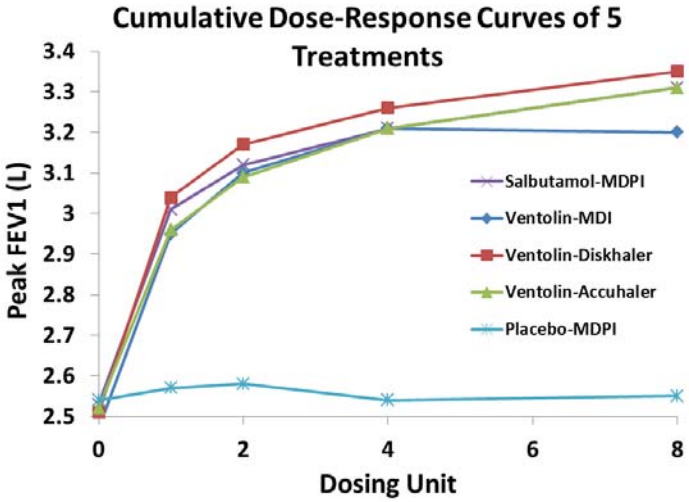

Fig.4.1 Least square mean peak FEV1 cumulative dose-response curve following dose-ascending, cumulative administration (1, 2, 4, 8 inhalations per treatment with dosing interval of 30 minutes). The dosing unit for Salbutamol-MDPI (purple) and Ventolin-MDI (blue) were 100 µg. The dosing unit for

Ventolin Diskhaler (brown) and Ventolin Accuhaler (green) were 200 µg. Only lactose carrier was delivered in placebo group (cyan). (Source: Table 1, 2, 3, 4 and 5)

The time-response curves of the first dose per treatment were also similar for Salbutamol-MDPI, Ventolin-MDI, Ventolin-Diskhaler, and Ventolin Accuhaler (Fig.4.2). By visual check, they all achieved maximal effect around 5-10 minutes post- first dose. The time-response curve of placebo seems remained at baseline level within 30 minutes post-first dose.

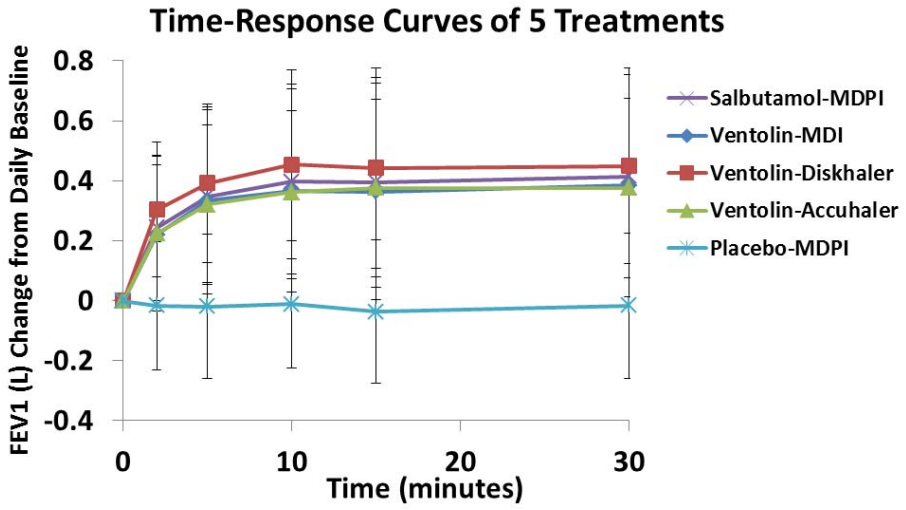

Fig.4.2 Arithmetic mean FEV1 change from daily baseline within 30 minutes following the first dose of each treatment. The FEV1 values were measured at 2, 5, 10, 15 and 30 minutes post-first dose. The dosing unit for Salbutamol-MDPI (purple) and Ventolin-MDI (blue) were 100 µg. The dosing unit for Ventolin Diskhaler (brown) and Ventolin Accuhaler (green) were 200 µg. Only lactose carrier was delivered in placebo group (cyan). Error bars represent the standard deviation. (Source: reviewer's analysis based on CSR IX-100-076 page 95 to 99, Table 14.2.12.1 to 14.2.12.5)

Conclusions:
The study demonstrated equivalence between Salbutamol-MDPI and each of Ventolin albuterol (Ventolin-MDI, Ventolin Diskhaler, and Ventolin Accuhaler) following dose-ascending, cumulative administration with respect to the primary endpoint (peak FEV1). The 95% confidence intervals of the ratios (salbutamol/reference) were within ± 20% of the peak FEV1 at each dose level.

The comparisons between Salbutamol-MDPI and placebo-MDPI showed that Salbutamol-MDPI was superior to placebo. The upper boundary of 95% confidence intervals were greater than 20% of the placebo peak FEV1 at cumulating dose of 200 µg, 400 µg and 800 µg, respectively.

Reviewer's comments:
According to the primary objectives and pre-defined endpoints, Salbutamol-MDPI was equivalent to Ventolin-MDI from the study results per se. However, the supportability of this Phase 2 efficacy study is limited, as 1) the inhalation device used in this study (b) (4) *was not the to-be marketed device; 2) this is not a double-blind study.*

It seems that most descriptions and the results of the primary endpoint were consistent in the report (report-body-076.pdf) except on page 27, under 9.7 statistical methods planned in the protocol and determination of sample size, the subtraction of pre-dose baseline was mentioned:

"The primary outcome variable for each treatment was to be the FEV1, dose response curve constructed from the FEV1 responses at each dose level. The FEV1 response at each dose level was the average of the two pre-dose determinations subtracted from the maximum FEV1 determination observed between 0-30 minutes post-dose."

The subtraction was not mentioned and implemented during data analysis according to the final results. It's likely that the above paragraph was transplanted from other studies without careful editing.

4.1.2 Study ABS-AS-101

Study Type: Phase 1 PK, PD, efficacy, and safety cumulative dose study in asthma adults

Title: Cumulative Dose Comparison of the Efficacy and Safety of Albuterol (b) (4) and ProAir HFA in Adult Patients with Asthma

Objective:
The primary objective was to compare the efficacy of inhaled Albuterol (b) (4) and inhaled ProAir HFA after a cumulative dose of 1440 µg administered as 1+1+2+4+8 inhalations of 90 µg per inhalation.

The secondary objective was to compare the safety, PK, and PD (extra-pulmonary) effects of inhaled Albuterol (b) (4) and inhaled ProAir HFA after a cumulative dose of 1440 µg.

Study Design and Method:
This investigation was Phase 1, multi-center, randomized, double-blind, double-dummy, cumulative-dose, two-period, crossover study in subjects (18 to 45 years of age) with persistent asthma. Cumulative dose of 1440 µg albuterol was administered via either Albuterol (b) (4) or ProAir HFA during each period. The washout period between two periods was 3 to 14 days. Total 47 subjects were randomized for efficacy, safety and initial PD assessment; 24 of them participated in the PK sub-study.

Noteworthy inclusion criteria:

- Asthma (FEV1 50 to 80% predicted for age, height, gender, and race per the National Health and Nutrition Examination Survey [NHANES] III reference values [Hankinson 1999]) of a minimum of 6 months duration that was stable for at least 30 days prior to the screening visit as defined by clinical history.
- Took inhaled corticosteroids (ICS) for persistent asthma at a stable, low to medium dose (the equivalent of no more than 500 mcg/day of fluticasone propionate) for 4 weeks or more with no history or current evidence of a clinically significant concomitant disease.
- Demonstrated reversible bronchoconstriction consisting of a ≥ 15% increase from baseline FEV1 within 30 minutes after 2 inhalations (180 mcg) of albuterol with ProAir HFA MDI (90 mcg).
- Non-smoker for at least 1 year prior to the SV and a maximum smoking history of 10 pack-years.

The dosing regimens of two treatments were:

- Test product (Albuterol (b) (4) cumulative dose of 1440 µg albuterol (1, 2, 4, 8, 16 inhalations with 90 µg each actuation and dosing interval was 30 minutes).
- Reference product (ProAir HFA): cumulative dose of 1440 µg albuterol (1, 2, 4, 8, 16 inhalations with 90 µg each actuation and dosing interval was 30 minutes).

During each treatment period, PK samples were collected at pre-dose (within 30 minutes prior to the first dosing), 15 minutes post-dosing following each of the first four cumulative doses (1, 2, 4, and 8

inhalations), and following the fifth (final) cumulative dose (16 inhalations) at 15 and 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours. Approximately 6 mL blood volume was required for each sample with total blood volume approximately 90 mL per period. All values below the lower limit of quantitation (BLQ) were considered as zero during the PK and statistical analyses.

Primary Endpoints:
Efficacy:!!

- Primary endpoint:!Baseline-adjusted FEV1 at 30 minutes after each of the five cumulative doses
- Secondary endpoint: Baseline-adjusted FEV1 area under the curve from 0 to 6 hours (AUC_{0-6}) following the administration of the final dose.

PK: AUC_{0-t}, C_{max}, T_{max}

PD:

- QTc interval at 15 minutes after each cumulative dose and then 0.5, 1, 2, 3, and 4 hours following the last cumulative dose
- plasma glucose concentrations at 15 minutes after each cumulative dose and then 0.5, 1, 2, 3, and 4 hours following the last cumulative dose
- plasma potassium concentrations at 15 minutes after each cumulative dose and then 0.5, 1, 2, 3, and 4 hours following the last cumulative dose
- Vital signs (blood pressure and heart rate) at 15 minutes after each cumulative dose and then 0.5, 1, 2, 3, 4, 5, and 6 hours following the last cumulative dose

Safety:

Some safety assessments (serial vital signs, corrected QT [QTc] intervals from serial ECGs, and serial glucose and potassium concentrations) were considered as PD endpoints.

Hypothesis:

- Efficacy primary endpoint (baseline-adjusted FEV1 at 30 minutes after each cumulative dose)
  H_0: $|\mu_{(b)(4)} - \mu_{ProAir}| > 0.20$ L for at least one of the cumulative doses
  (90% CI for the difference in treatment means for the change from baseline in FEV1 30 minutes post-dose after each cumulative dose were all within the limits ± 0.20 L)

  H_1: $|\mu_{(b)(4)} - \mu_{ProAir}| < 0.20$ L for all of the cumulative doses.

  For the efficacy secondary endpoint (baseline-adjusted FEV1 AUC_{0-6}, the treatments were considered equivalent if the 90% CI for the mean difference in the baseline adjusted FEV1 AUC_{0-6} following the final cumulative dose was contained entirely within the limits ± 1.2 L·hr.

- PK
  AUC_{0-t} was calculated from time zero to the last measurable plasma concentration using the linear trapezoidal rule. C_{max} was obtained from the observed data. The exposure with Albuterol (b) (4) was considered no higher if the upper limit of the two-sided 90% CI was less than 1.25.

Bioanalytical Method:
Plasma samples were analyzed by HPLC-MS/MS with LLOQ at 2.00 pg/mL. The calibration curves of undiluted samples were linear over the range of concentrations from 2.00 to 1000.0 pg/mL albuterol. The intra batch (n=6) precision and accuracy were 4.44% (CV) and -5.00% (bias) at 6.00 pg/mL, respectively.

Exclusion of Subjects in Site 3733 from Analysis:
Due to the pre-defined criteria, the initial numbers of subjects (initial population) included in the initial efficacy/PD and PK analysis were 47 and 22, respectively (subject 1007 and 1017 at Site 3733 were excluded from PK analysis due to insufficient samples and high pre-dose concentration, respectively). However, after the data for the initial population were analyzed and unblinded, it was observed that the PK data from Site 3733 displayed aberrant plasma profiles that deviated from the known PK characteristics of albuterol. Specifically, for all 8 subjects at Site 3733, their plasma albuterol levels remained well above the elimination curve at 12 hours after the final dose.

The Sponsor could not conclusively identify the cause of the aberrant plasma profiles from Site 3733 and a contaminating source of albuterol could alter any result that was based on a biological response, a decision was made at a post-unblinding data review meeting to exclude all data from Site 3733 in the primary analyses of efficacy, PD, and PK outcome measures and to repeat the study analyses with the re-defined populations (primary population). Thus the numbers of subjects (primary population) included in the primary efficacy/PD and PK analysis were 39 and 16, respectively.

Efficacy Results:

Primary end point:

Subjects in each treatment sequence were similar with respect to baseline FEV1 characteristics and data were comparable to all randomized subjects (including Site 3733) (Table 4.6).

Table 4.6 Baseline FEV1 Characteristics by Treatment Sequence and Device Order at Screening (Randomized Subjects) (Excludes Data from Site 3733)

	Qualifying % Predicted FEV1	Qualifying FEV1	Post FEV1	% Reversibility
Sequence	N Mean(SD)	N Mean(SD)	N Mean(SD)	N Mean(SD)
SPX-PRO	21 65.3 (7.74)	21 2.50 (0.607)	25 3.04 (0.631)	21 26.6 (10.7)
PRO-SPX	18 66.1 (8.21)	18 2.49 (0.509)	22 3.09 (0.526)	18 23.8 (8.79)
Overall	39 65.7 (7.87)	39 2.49 (0.557)	47 3.06 (0.578)	39 25.3 (9.83)

(Source: CSR ABS-AS-101 page 193, Table 14.1.5.2)

Following inhalation of 1440 µg cumulative dose of albuterol, a cumulative dose-response relationship was observed for each product by visual check (Fig.4.3). The differences of least square means of baseline-adjusted FEV1 between two products (Albuterol (b) (4) – ProAir HFA) were -0.06 (90% CI = -0.12, 0.01), -0.07 (90% CI = -0.13, 0.00), -0.07 (90% CI = -0.13, 0.00), -0.05 (90% CI = -0.11, 0.02), and -0.03(90% CI = -0.10, 0.03) at cumulative dose of 90 µg, 180 µg, 360 µg, 720 µg, and 1440 µg, respectively (Table 4.7). The 90% CI of mean difference for each cumulative dose was contained within the predefined 0.2 L, therefore the H_0 hypothesis was rejected and H_1 hypothesis was accepted.

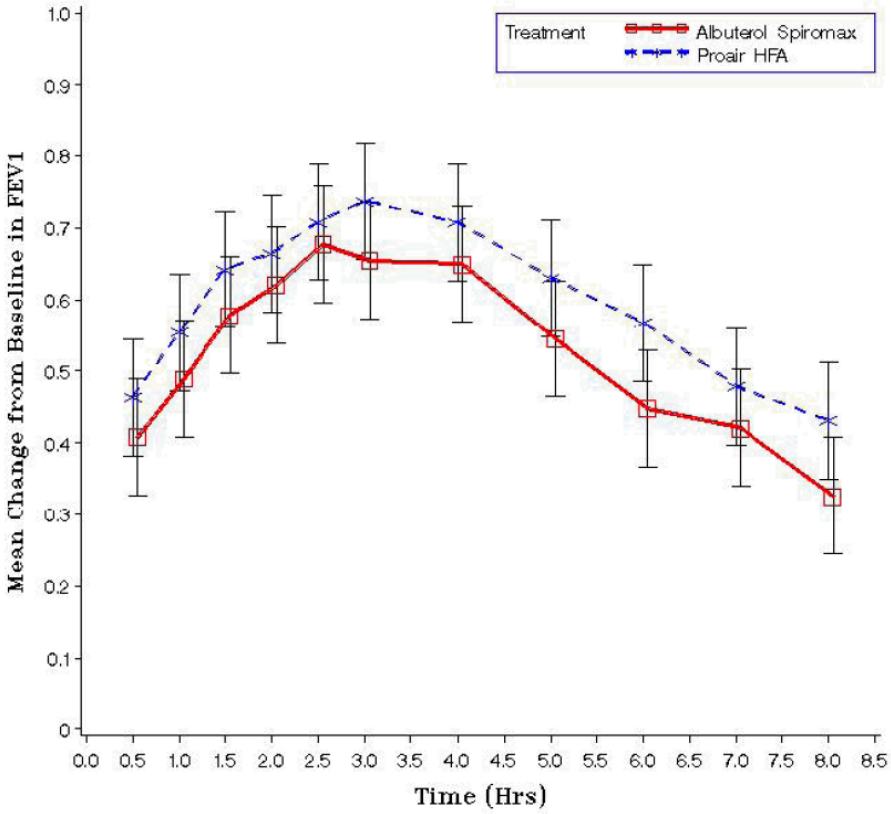

Fig.4.3 Least square mean change from baseline in FEV1 following inhalation of 1440 µg cumulative dose of albuterol (1, 2, 4, 8, 16 inhalations with 90 µg each actuation with dosing interval as30 minutes)/ ! Error bars represent the standard error. (Source: CSR ABS-AS-101 page 81, Figure 3)

Table 4.7 Change from Baseline in FEV1 (L) 30 Minutes after Each of the Five Cumulative Doses

Cumulative Doses (µg)	Albuterol (b) (4) (T)*	ProAir HFA (R)*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	0.42 (0.076, 38)	0.48 (0.076, 38)	-0.06	-0.12	0.01
180	0.50 (0.076, 38)	0.57 (0.076, 37)	-0.07	-0.13	0.00
360	0.59 (0.076, 38)	0.66 (0.076, 38)	-0.07	-0.13	0.00
720	0.63 (0.076, 38)	0.68 (0.076, 38)	-0.05	-0.11	0.02
1440	0.69 (0.076, 38)	0.72 (0.076, 38)	-0.03	-0.10	0.03

*** Lease square mean (standard error, N)**
Estimated means, standard errors (SE), and CIs derived from a linear mixed model with fixed effects for treatment (device), sequence, period, pooled site, cumulative dose, treatment by cumulative dose, baseline FEV1 as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 82, Table 14)

Secondary end point:
The differences of least square means of Baseline-adjusted FEV1 $AUC_{0\text{-}6}$ (L·hr) following the final cumulative dose (Albuterol (b) (4) – ProAir HFA) was -0.48 (90% CI = -0.75, -0.20) (L·hr) (Table 4.8). The 90% CI of mean difference was contained within the predefined 1.2 L·hr, therefore the H_0 hypothesis was rejected and H_1 hypothesis was accepted.

Table 4.8 Baseline-adjusted FEV1 AUC_{0-6} Following the Final Cumulative Dose

	Albuterol (b) (4) (T)	ProAir HFA (R)	Difference (T-R)	90% CI lower limit	90% CI upper limit
AUC_{0-6} (L·hr)	3.83 (0.595, 38)*	4.30 (0.595, 38)*	-0.48	-0.75	-0.20

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline FEV1 as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 85, Table 16)

PK Results:
Two centers carried out PK sub-study, in which there were 16 and 8 patients assigned to center 3249 and center 3733, respectively. It seems that regardless what device was involved, albuterol plasma concentrations from center 3733 remained stable during the later elimination phase for both ProAir HFA and Albuterol (b) (4) (Fig.4.4). The Sponsor's proposal to exclude 8 patients in Site 3733 from PK analysis appears reasonable.

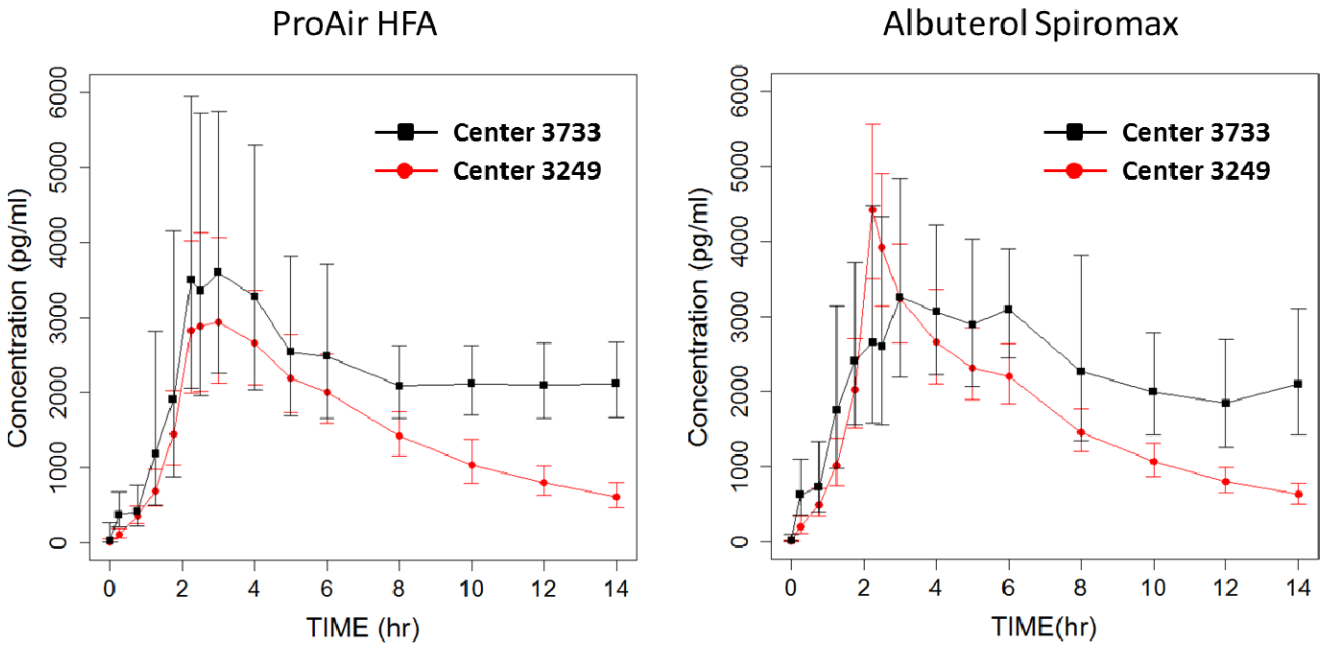

Fig.4.4 Geometric mean albuterol concentration-time profiles of ProAir HFA (left) and Albuterol (b) (4) (right) measured from center 3733 (black square) and center 3294 (red circle) following inhalation of 1440 µg cumulative dose of albuterol. Error bars represent the standard deviation (concentration of BLQ was set at 1/2 of the value of LLOQ). (Source: reviewer's analysis)

Following inhalation of 1440 µg cumulative dose of albuterol, the ratios (Albuterol (b) (4) ProAir HFA, N=16) of least-squares geometric mean AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively (Table 4.9 and Fig. 4.5). Albuterol median T_{max} from Albuterol (b) (4) was approximately 34 minutes earlier than ProAir HFA.

Table 4.9 Comparison of PK Parameters between Albuterol (b) (4) and ProAir HFA Following Inhalation of Cumulative dose of 1440 µg Albuterol (N=16)

Parameter	Statistic	Albuterol *Spiromax*	*ProAir* HFA
AUC_{0-t} [1,2] (pg*hr/mL)	N	16	16
	Geometric Mean	23227	20939
	95% CI	(20833, 25896)	(18781, 23345)
	Treatment Ratio: *Spiromax/ProAir*		
	Ratio	1.109	
	90% CI	(1.04, 1.19)	
$C_{max,}$ [1,2] (pg/mL)	N	16	16
	Geometric Mean	4422.8	3303.8
	95% CI	(3861, 5066)	(2884, 3784)
	Treatment Ratio: *Spiromax/ProAir*		
	Ratio	1.339	
	90% CI	(1.17, 1.53)	
T_{max} [3] (hr)	N	16	16
	Mean (SD)	2.48 (0.087)	3.05 (0.584)
	Median	2.48	3.04

[1] **Estimated geometric means and CIs derived from a log-linear mixed model with fixed effects for sequence, treatment (device), period, site, and random effect for subject.**

(Source: CSR ABS-AS-101 page 94, Table 20)

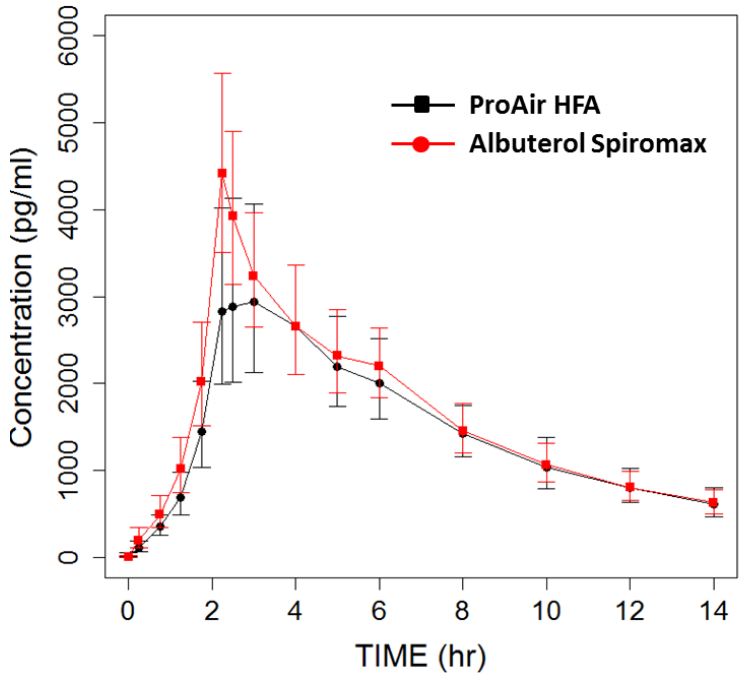

Fig.4.5 Geometric mean albuterol concentration-time profiles of ProAir HFA (Black) and Albuterol (b) (4) (red) following inhalation of 1440 µg cumulative dose of albuterol (N=16). Error bars represent the standard deviation (concentration of BLQ was set at 1/2 of the value of LLOQ). (Source: reviewer's analysis)

PD Results:

QTc

There was an overall increase in mean QTcB following administration of both products. The increase peaked at 30 minutes after the last cumulative dose; thereafter mean QTcB decreased in both treatment groups, but had not returned to baseline by the 4-hour post-dose time point in both treatment groups (Fig.4.6). 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 (Fig.4.7).

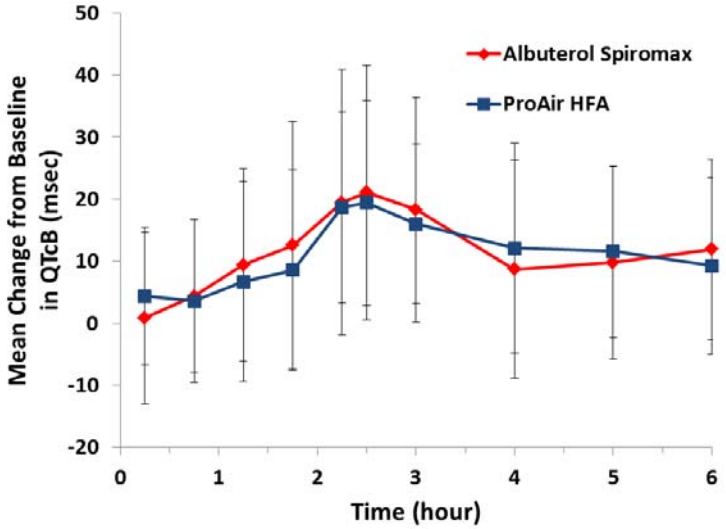

Fig.4.6 Arithmetic mean change from baseline in QTcB (msec) following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol (b) (4) (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 108, Figure 7)

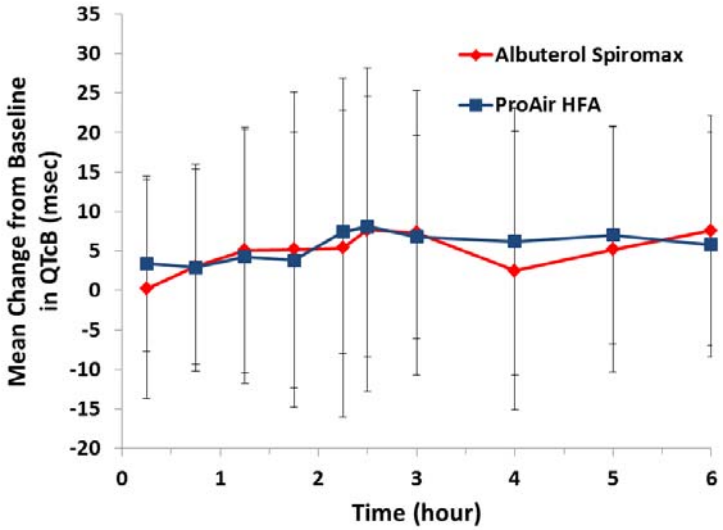

Fig.4.7 Arithmetic mean change from baseline in QTcF (msec) following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol (b) (4) (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 109, Figure 8)

The differences of mean change from baseline in QTc intervals between two products were less than 4 msec at all 15-minute post-dose time points by either QTcB (Table 4.10) or QTcF method (Table 4.11). The upper limits of the 90% CIs for the treatment differences did not exceed 10 msec for any cumulative dose.

Table 4.10 Mean Change from Baseline in QTcB intervals (msec) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol (b) (4) (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	2.44 (2.53, 37)	5.70 (2.49, 38)	-3.25	-7.82	1.31
180	5.88 (2.53, 37)	5.48 (2.51, 37)	0.41	-4.18	5.00
360	10.83 (2.52, 37)	8.03 (2.49, 38)	2.79	-1.76	7.35
720	13.83 (2.50, 38)	9.92 (2.49, 38)	3.91	-0.62	8.44
1440	20.75 (2.50, 38)	20.47 (2.54, 36)	0.28	-4.30	4.87

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline ECG QTcB as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 110, Table 26)

Table 4.11 Mean Change from Baseline in QTcF intervals (msec) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol (b) (4) (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	1.37 (2.10, 37)	4.47 (2.06, 38)	-3.11	-7.21	1.00
180	4.18 (2.09, 37)	4.37 (2.08, 37)	-0.19	-4.31	3.93
360	6.33 (2.09, 37)	5.46 (2.06, 38)	0.87	-3.22	4.97
720	6.22 (2.06, 38)	4.90 (2.06, 38)	1.31	-2.76	5.39
1440	6.43 (2.06, 38)	8.73 (2.10, 36)	-2.30	-6.42	1.82

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline ECG QTcF as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 110, Table 26)

Maximum and weighted mean changes from baseline in QTcB and QTcF intervals over 4-hour period after the final cumulative dose were estimated. The difference between two products were less than 3 msec for both maximum and weighted mean changes (Table 4.12)

Table 4.12 Maximum and Weighted Mean Changes in QTcB and QTcF Intervals (msec) Over 4 Hours after the Final Cumulative Dose

	QTcB	QTcF
Maximal mean change from Baseline (msec)	2.63 (90% CI = -2.40, 7.66, N=38)	0.91 (90% CI = -2.83, 4.65, N=38)
Weighted mean change from Baseline (msec)	-0.42 (90% CI = -4.08, 3.23, N=38)	-1.27 (90% CI = -4.18, 1.64, N=38)

Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline respective ECG value as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 112, Table 27)

Plasma Glucose Concentrations

There was an increase in mean plasma glucose concentrations following administration of both products. The increase peaked at 30 minutes after the last cumulative dose; thereafter mean plasma glucose concentrations returned to baseline over the ensuing 3.5 hours in both groups (Fig.4.8).

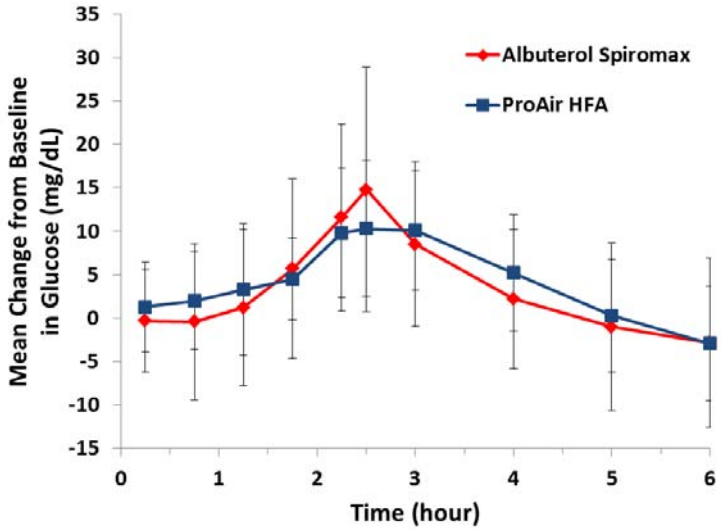

Fig.4.8 Arithmetic mean change from baseline in plasma glucose concentration (mg/dL) following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol (b) (4) (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 97, Figure 5)

The differences in plasma glucose concentration mean changes from baseline between two treatments were less than 3 mg/dL at each of the 15-minute post-dose time points (Table 4.13). In addition, the limits of the 90% CIs for the comparison of treatment differences did not exceed 5 mg/dL for any cumulative dose.

Table 4.13 Mean Change from Baseline in Plasma Glucose Concentrations (mg/dL) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol (b) (4) (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	0.34 (1.25, 37)	0.20 (1.28, 36)	0.13	-2.37	2.63
180	0.10 (1.26, 36)	1.04 (1.29, 35)	-0.94	-3.45	1.57
360	1.77 (1.27, 36)	5.46 (2.06, 38)	-0.87	-3.40	1.65
720	5.90 (1.25, 37)	4.90 (2.06, 38)	1.86	-0.62	4.33
1440	11.35 (1.27, 36)	8.73 (2.10, 36)	2.26	-0.26	4.78

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline glucose as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 99, Table 22)

The difference (Albuterol (b) (4) - ProAir HFA) of maximum and weighted mean changes from baseline in plasma glucose concentrations over 4-hour period after the final cumulative dose were 3.80 (90% CI = 0.04, 7.55) mg/dL and 0.51 (90% CI = -1.52, 2.53) mg/dL, respectively (Table 4.14).

Table 4.14 Maximum and Weighted Mean Changes in Plasma Glucose Concentrations (mg/dL) Over 4 Hours after the Final Cumulative Dose

	Albuterol (b) (4) (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
Maximal mean change from Baseline (mg/dL)	17.21 (1.65, 37)	13.42 (1.71, 36)	3.80	0.04	7.55
Weighted mean change from Baseline (mg/dL)	4.17 (1.01, 37)	3.67 (1.05, 36)	0.51	-1.52	2.53

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline glucose as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 101, Table 23)

Plasma Potassium Concentrations

There was a decrease in mean plasma potassium concentrations following administration of both products. The reduction trough reached at approximately 15 to 30 minutes following the last cumulative dose; thereafter mean plasma potassium concentrations returned to baseline over the ensuing 3.5 hours in both treatment groups (Fig.4.9).

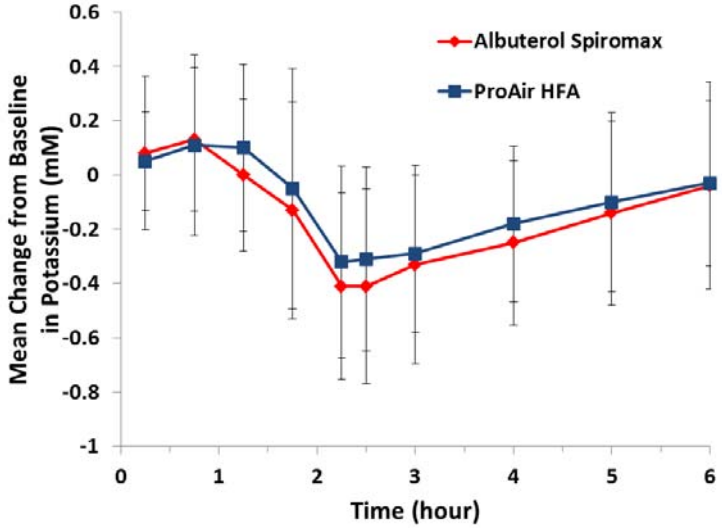

Fig.4.9 Arithmetic mean change from baseline in plasma potassium concentration following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol (b) (4) (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 103, Figure 6)

!

The differences in plasma potassium concentrations mean changes from baseline between two treatments were less than 0.1 mM at each of the 15-minute post-dose time points (Table 4.15). In addition, the limits of the 90% CIs for the comparison of treatment differences did not exceed 0.2 mM for any cumulative dose.

Table 4.15 Mean Change from Baseline in Plasma Potassium Concentrations (mM) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol [redacted] (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	0.08 (0.05, 37)	0.03 (0.05, 37)	0.05	-0.06	0.16
180	0.13 (0.05, 36)	0.11 (0.05, 35)	0.02	-0.09	0.13
360	-0.01 (0.05, 36)	0.08 (0.05, 35)	-0.08	-0.19	0.03
720	-0.13 (0.05, 37)	-0.07 (0.05, 37)	-0.06	-0.17	0.05
1440	-0.41 (0.05, 35)	-0.34 (0.05, 36)	-0.07	-0.19	0.04

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline potassium as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 104, Table 24)

The difference (Albuterol [redacted] - ProAir HFA) of minimum and weighted mean changes from baseline in plasma potassium concentrations over 4-hour period after the final cumulative dose were -0.08 (90% CI = 0.19, 0.02) mM and -0.03 (90% CI = -0.12, 0.05) mM, respectively (Table 4.16).

Table 4.16 Mean Minimum and Weighted Mean Changes in Plasma Potassium Concentrations (mM) Over 4 Hours after the Final Cumulative Dose

	Albuterol [redacted] (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
Mean Minimum Change from Baseline (mM)	-0.54 (0.047, 37)	-0.46 (0.047, 37)	-0.08	-0.19	0.02
Weighted mean Change from Baseline (mM)	-0.22 (0.042, 37)	-0.19 (0.042, 37)	-0.03	-0.12	0.05

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline potassium as a covariate, and a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 105, Table 25)

Diastolic Blood Pressure

There was an overall, small decrease in mean diastolic blood pressure following administration of both products. There was a gradually increase of mean diastolic blood pressure once the trough was reached, but the diastolic blood pressure had not returned to baseline by the 6-hour post-dose time point in both treatment groups (Fig. 4.10).

The differences in diastolic blood pressure mean changes from baseline between two treatments were less than 3 mmHg at each of the 15-minute post-dose time points (Table 4.17). In addition, the limits of the 90% CIs for the comparison of treatment differences did not exceed 5 mmHg for any cumulative dose.

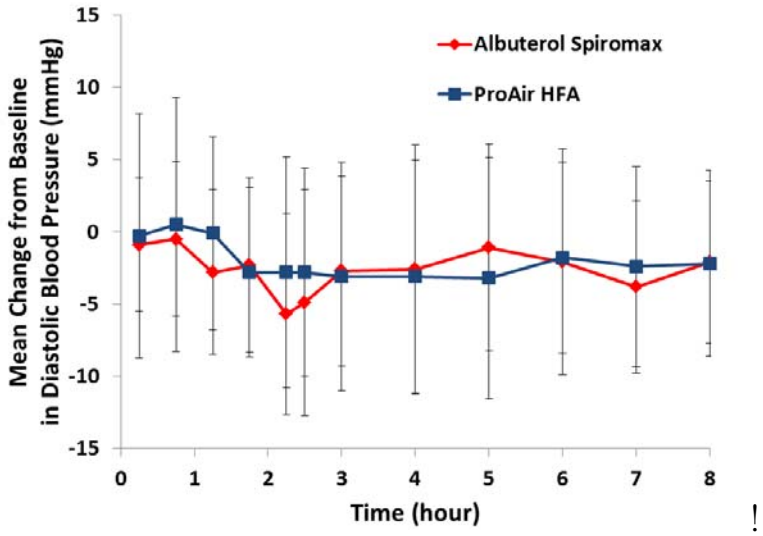

Fig.4.10 Arithmetic mean change from baseline in diastolic blood pressure following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol Spiromax (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 103, Figure 6)

Table 4.17 Mean Change from Baseline in Diastolic Blood Pressure (mmHg) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	0.56 (1.10, 38)	0.14 (1.10, 38)	0.42	-1.63	2.47
180	0.61 (1.10, 38)	1.30 (1.10, 38)	-0.69	-2.74	1.37
360	-2.07 (1.10, 38)	0.69 (1.10, 38)	-2.77	-4.81	-0.72
720	-1.73 (1.11, 38)	-2.25 (1.10, 38)	0.51	-1.54	2.57
1440	-5.00 (1.10, 38)	-2.32 (1.10, 38)	-2.69	-4.74	-0.63

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline diastolic BP as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 116, Table 28)

The difference (Albuterol Spiromax - ProAir HFA) of minimum and weighted mean change from baseline in diastolic blood pressure over 6-hour period after the final cumulative dose were -2.51 (90% CI = -4.14, -0.89) mmHg and 0.25 (90% CI = -0.98, 1.48) mmHg, respectively (Table 4.18).

Table 4.18 Mean Minimum and Weighted Mean Decrease in Diastolic Blood Pressure (mmHg) Over 6 Hours after the Final Cumulative Dose

	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
Mean Minimum Change from Baseline (mmHg)	-11.0 (1.03, 38)	-8.44 (1.03, 38)	-2.51	-4.14	-0.89
Weighted mean Change from Baseline (mmHg)	-1.88 (0.806, 38)	-2.13 (0.805, 38)	0.25	-0.98	1.48

*** Lease square mean (standard error, N)**

Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline respective vital sign as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 118, Table 29)

Systolic Blood Pressure

There was an overall, moderate increase in mean systolic blood pressure following administration of both products. The increase peaked at 15 minutes after the last cumulative dose. The systolic blood pressure remained relative stable and did not return to baseline by the 6-hour post-dose time point in both treatment groups (Fig. 4.11).

The differences in systolic blood pressure mean changes from baseline between two treatments were less than 3 mmHg at each of the 15-minute post-dose time points except for the highest cumulative dose (1440 µg) (Table 4.19). In addition, the limits of the 90% CIs for the comparison of treatment differences did not exceed 5 mmHg for any cumulative dose except for the highest cumulative dose (1440 µg).

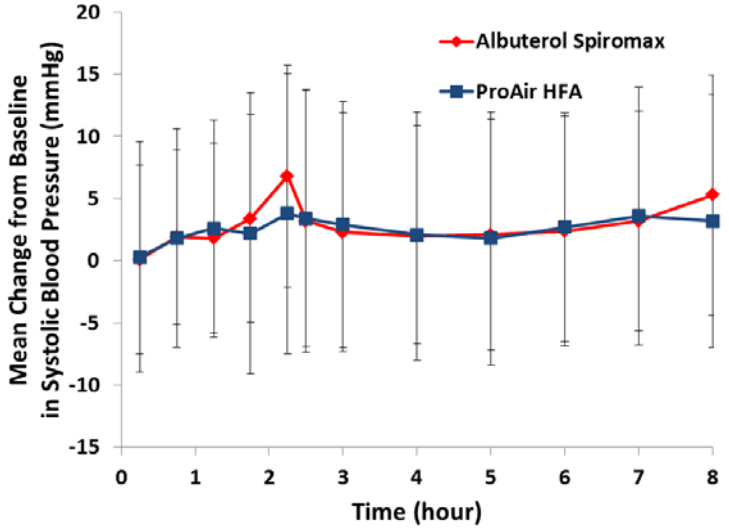

Fig.4.11 Arithmetic mean change from baseline in systolic blood pressure following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol Spiromax (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 120, Figure 10)

Table 4.19 Mean Change from Baseline in Systolic Blood Pressure (mmHg) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	2.29 (1.47, 38)	1.83 (1.46, 38)	0.46	-1.85	2.78
180	3.78 (1.46, 38)	3.54 (1.46, 38)	0.24	-2.07	2.55
360	3.71 (1.46, 38)	4.42 (1.46, 38)	-0.71	-3.01	1.60
720	5.02 (1.46, 38)	3.76 (1.46, 38)	1.26	-1.05	3.57
1440	8.67 (1.47, 38)	5.36 (1.46, 38)	3.32	1.00	5.63

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline systolic BP as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 121, Table 30)

The difference (Albuterol Spiromax - ProAir HFA) of maximum and weighted mean changes from baseline in systolic blood pressure over 6-hour period after the final cumulative dose were 0.14 (90% CI = -2.83, 3.12) mmHg and 0.17 (90% CI = -1.64, 1.99) mmHg, respectively (Table 4.20).

Table 4.20 Maximum and Weighted Mean Changes in Systolic Blood Pressure (mmHg) Over 6 Hours after the Final Cumulative Dose

	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
Maximal mean change from Baseline	13.31 (1.38, 38)	13.17 (1.38, 38)	0.14	-2.83	3.12
Weighted mean change from Baseline	4.44 (1.06, 38)	4.27 (1.05, 38)	0.17	-1.64	1.99

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline respective vital sign as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 123, Table 31)

Heart Rate

There was an overall increase in mean heart rate following administration of both products. The increase peaked at 15 to 30 minutes after the administration of the last cumulative dose; thereafter mean heart rate gradually reduced to the level close to the baseline around 4 hours after the administration of the last cumulative dose. There was a trend for mean heart rate increasing again afterwards for both products (Fig. 4.12).

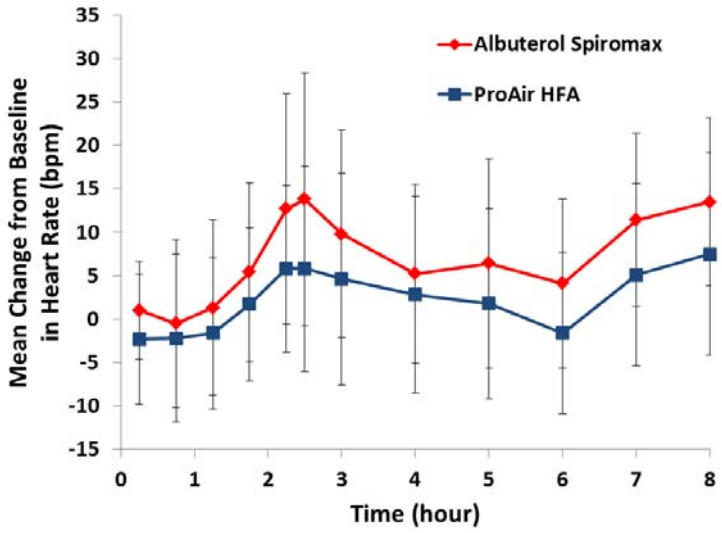

Fig.4.12 Arithmetic mean change from baseline in heart rate following inhalation of 1440 µg cumulative dose of albuterol via either Albuterol Spiromax (red) or ProAir HFA (blue). Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-101 page 125, Figure 11)

The differences in mean heart rate changes from baseline between two treatments were less than 2 bpm at each of the 15-minute post-dose time points except for the highest cumulative dose (1440 µg) (Table 4.21). In addition, the limits of the 90% CIs for the comparison of treatment differences did not exceed 5 bpm for any cumulative dose except for the highest cumulative dose (1440 µg).

Table 4.21 Mean Change from Baseline in Heart Rate (bpm) at 15 Minutes after Each of Five Cumulative Doses

Cumulative Doses (µg)	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
90	0.67 (1.67, 38)	-0.80 (1.66, 38)	1.48	-1.06	4.01
180	-0.74 (1.68, 38)	-0.53(1.67, 38)	-0.21	-2.76	2.34
360	0.38 (1.68, 38)	-0.12 (1.66, 38)	0.50	-2.03	3.04
720	4.56(1.68, 38)	3.07(1.67, 38)	1.50	-1.05	4.04
1440	12.01 (1.68, 38)	7.50 (1.67, 38)	4.51	1.95	7.06

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, treatment (device), period, pooled center, cumulative dose, treatment by cumulative dose, baseline heart rate as a covariate, a random effect for subject, and an AR(1) correlation for repeated observations within subject.
(Source: adapted from CSR ABS-AS-101 page 126, Table 32)

The difference (Albuterol Spiromax - ProAir HFA) of maximum and weighted mean changes from baseline in heart rate over 6-hour period after the final cumulative dose were 4.57 (90% CI = 1.87, 7.27) bpm and 2.44 (90% CI = 0.75, 4.12) bpm, respectively (Table 4.22).

Table 4.22 Maximum and Weighted Mean Changes in Heart Rate (bpm) Over 6 Hours after the Final Cumulative Dose

	Albuterol Spiromax (T)*	ProAir HFA*	Difference (T-R)	90% CI lower limit	90% CI upper limit
Maximal mean change from Baseline (bpm)	19.78 (2.32, 38)	15.21 (2.31, 38)	4.57	1.87	7.27
Weighted mean change from Baseline (bpm)	6.90 (1.75, 38)	4.46 (1.75, 38)	2.44	0.75	4.12

*** Lease square mean (standard error, N)**
Estimated means, SEs, and CIs derived from a linear mixed model with fixed effects for sequence, period, pooled site, treatment, baseline respective vital sign as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-101 page 128, Table 33)

Conclusions:
Efficacy: Following inhalation of 1440 µg cumulative dose of albuterol, the least square mean of baseline-adjusted FEV1 at 30 minutes after each cumulative dose was equivalent between Albuterol Spiromax and ProAir HFA with a slight numerical advantage for ProAir HFA (0.03 L to 0.07 L greater). The least square mean of Baseline-adjusted FEV1 AUC_{0-6} following the final cumulative dose was equivalent between Albuterol Spiromax and ProAir HFA with a slight numerical advantage for ProAir HFA (0.48 L·hr greater).

PK: Following inhalation of cumulative dose of 1440 µg albuterol, AUC_{0-t} was equivalent between two products; Albuterol Spiromax C_{max} was approximately 34% higher than that of ProAir HFA; Albuterol Spiromax median T_{max} was approximately half an hour earlier than that of ProAir HFA.

PD:
The summary of differences between two treatments according to studied PD parameters was listed as Table 1.2.

Overall the PD responses were similar between Albuterol Spiromax and ProAir HFA at each of the 15-minute post-dose time points up to cumulative dose of 720 µg albuterol. The mean treatment differences were numerically small. The treatment differences became statistically significant for vital signs (blood pressures and heart rate) mean changes at cumulative dose of 1440 µg albuterol. During post-final-dose monitoring period (6 hours for vital sign and 4 hours for lab test), it seems that the differences of maximal mean changes for plasma glucose concentration, diastolic blood pressure and heart rate were statistically significant. The difference of weighted mean changes for heart rate was also statistically significant.

The differences on PD responses between Albuterol Spiromax and ProAir HFA were presented during mid-cycle meeting held on 10/8/2014. Medical reviewer Dr. Keith Hull considered the differences were generally small and might not be clinically meaningful.

Reviewer's comments:
In accordance with the Sponsor pre-defined efficacy primary and secondary endpoint, Albuterol Spiromax and ProAir HFA were equivalent on efficacy following inhalation of 1440 µg cumulative dose of albuterol. The clinical meanings of the pre-defined boundary are reviewed by medical officer Dr. Keith Hull. The PK profiles between two products are overall similar, though the bioequivalence criterion was not reached. The boundaries of PD endpoints were not pre-defined for this study. Generally the differences of mean changes from baseline between two treatments were numerically small for both lab tests and vital signs; however the clinical meanings of these differences were not clear.

4.1.3 Study ABS-AS-201

Study Type: Phase 2 PD, efficacy, and safety single-dose-ranging study in asthma adults

Title: 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

Objective:
Primary Objective: To evaluate the efficacy of 2 doses of albuterol delivered via Albuterol Spiromax or ProAir HFA, relative to placebo.

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

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, double-dummy, single-dose, 5-treatment, 10-sequence, placebo-controlled, crossover comparison of the bronchodilator response to Albuterol Spiromax and ProAir HFA in male or female subjects (ages 12 and older) with persistent asthma. The washout period between treatments was 3 to 7 days. A follow-up visit was conducted 3 to 7 days after the last treatment or upon subject discontinuation. Total 71 subjects were randomized and treated with 68 completed the study. No PK samples were collected.

Noteworthy inclusion criteria:

- Persistent asthma for a minimum of 6 months duration that had been stable for at least 4 weeks prior to the screen visit. The asthma diagnosis was to be in accordance with the National Asthma Education and Prevention Program Guidelines.
- At the time of screening, FEV1 was within 50% to 80% predicted for age, height, gender and race per the National Health and Nutrition Examination Survey III reference values.

- Demonstration of reversible bronchoconstriction as verified by a >15% increase in FEV1 within 30 minutes following inhalation of 180 mcg of albuterol MDI.
- Were on a stable dose of inhaled corticosteroids (ICS) for at least 4 weeks prior to the screen visit and remained on the same dose for the duration of the study.
- Non-smokers for at least 12 months prior to the screen visit and maximum pack-year smoking history of 10 years.

The four single-dose active treatments were:
- 90 µg albuterol via Albuterol Spiromax
- 180 µg albuterol via Albuterol Spiromax
- 90 µg albuterol via ProAir HFA
- 180 µg albuterol via ProAir HFA

A double-blind/double-dummy procedure was used to blind treatments and dose levels. For each treatment, subjects received total 4 inhalations: 1) two inhalations with each inhalation from a separate Spiromax device and 2) two inhalations with each inhalation from a separate ProAir device.

Primary Endpoints:
Efficacy:
- The primary efficacy endpoint was the baseline-adjusted area-under-the effect curve for FEV1 observed up to 6 hours following completion of dosing (FEV1 $AUEC_{0-6}$), measured in liter hours (L·hr). Baseline was the study treatment day baseline.
- The secondary efficacy endpoint was baseline-adjusted area-under-the effect curve for percent-predicted FEV1 over 6 hours (PPFEV1 $AUEC_{0-6}$), measured in percent-predicted FEV1 hours (%·hr).
- Other endpoints:
  1. The baseline-adjusted maximum FEV1 (L) within 6 hours post-dose
  3. The baseline-adjusted maximum percent-predicted FEV1 (maxPPFEV1, %) within 6 hours post-dose
  4. The time (in minutes) to response onset, defined as the first time that an increase from baseline in FEV1 of at least 15% was noted in subjects who exhibited an increase in baseline FEV1 of at least 15% within 30 minutes post-dose
  5. The time (in minutes) to response onset, defined as the first time that an increase from baseline in FEV1 of at least 12% was noted in subjects who exhibited an increase in baseline FEV1 of at least 12% within 30 minutes post-dose
  6. The time (in minutes) to maximum FEV1 (i.e., time to peak)
  7. The duration of effect (offset), defined as time from onset of a 15% or greater increase in FEV1 to offset of the 15% increase in FEV1
  8. The duration of effect (offset), defined as time from onset of a 12% or greater increase in FEV1 to offset of the 12% increase in FEV1

The baseline for FEV1 evaluations on each treatment day was taken as the average of the 2 pre-dose FEV1 determinations on that day. Post-dose FEV1 were planned to be measured at 5, 15, 30, 45 minutes, then at 1, 2, 3, 4, 5, and 6 hours. The area under the FEV1 curve was calculated according to the trapezoidal rule and was based on actual (not scheduled) times of measurement of the FEV1. When time-related endpoints were evaluated, the actual time points of each FEV1 recording, but not the planned time points were utilized.

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

PD/Vital sings:

- The maximum change from baseline in systolic blood pressure
- The minimum change from baseline in diastolic blood pressure
- The maximum change from baseline in heart rate
- The weighted mean change from baseline in systolic and diastolic blood pressure and heart rate

Vital signs (blood pressure and heart rate) measurements were taken at baseline (pre-dose) and serially at 0.5, 1, 2, 3, 4, 5, and 6 hours post-dose.

Time points in analysis:
The study planned post-dose time points (0.083, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours) were used to evaluate primary and secondary endpoints. The actual post-dose time point (when FEV1 was measured for each individual at each visit) during the study was used to evaluate the time effects in other endpoints.

Demography:
The demographic characteristics for the 71 randomized subjects who received treatment (ITT population) are summarized in Table 4.23. This investigation included 3 children.

Table 4.23 Demographic Characteristics of Intend-To-Treat (ITT) Population

Demographic Characteristics	Total N=71 (100%)
Gender	
Female	41 (58%)
Male	30 (42%)
Race	
White	54 (76%)
Black	16 (23%)
Asian	1 (1%)
Age	
12 to <18	3 (4%)
18 to <65	64 (90%)
≥ 65	4 (6%)

(Source: adapted from CSR ABS-AS-201, page 58, Table 4)

Efficacy Results:

Primary endpoint

Mean Baseline FEV1 values were similar for each of the 5 treatment arms, ranging from 2.15 to 2.17 L (Table 4.24).

Following each single-dose, active treatment of albuterol inhalation, there was an overall increase in mean FEV1 at each 6-hour post-dose time point with peak mean FEV1 achieved approximately at 1 hour (Fig.4.13). The mean change from baseline FEV1 value was 0.05 L for placebo and ranged from 0.33 L to 0.40 L for the active groups at 1 hour post-dose.

Table 4.24 Mean (SD) of Baseline FEV1 (L) at Each Period by Treatment

!

Treatment	Subject N	Baseline FEV1 (L)*
Spiromax (90 ug)	68	2.17 (0.528)
Spiromax (180 ug)	68	2.15 (0.574)
ProAir HFA (90 ug)	70	2.15 (0.549)
ProAir HFA (180 ug)	68	2.17 (0.533)
Placebo	69	2.15 0.581)

*** Mean (SD)**
(Source: adapted from CSR ABS-AS-201, page 149, Table 14.2.1.1)

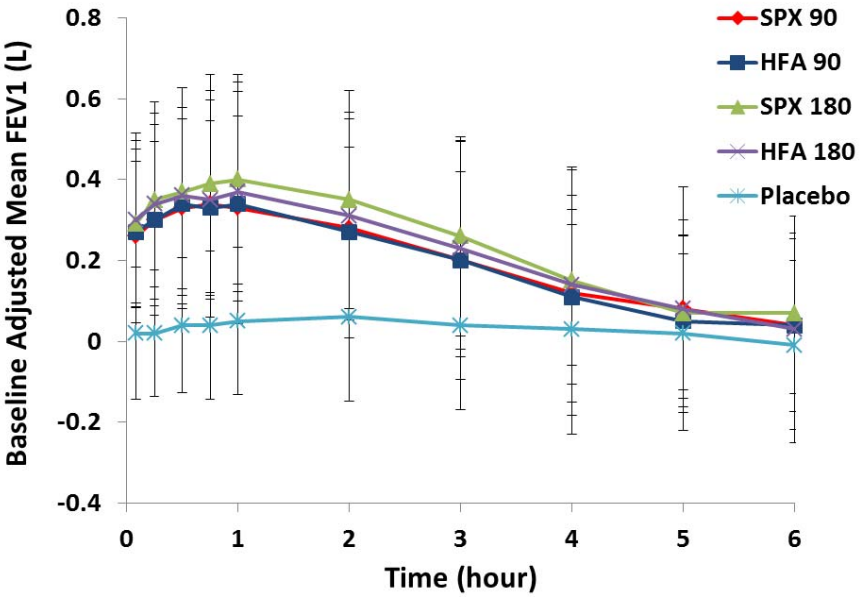

Fig.4.13 Arithmetic baseline-adjusted mean FEV1 following single-dose albuterol delivered as Albuterol Spiromax 90 µg (SPX90, red), Albuterol Spiromax 180 µg (SPX180, green), ProAir HFA 90 µg (HFA90, blue), ProAir HFA 180 µg (HFA180, purple), and placebo (P, cyan), respectively. Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-102 page 62, Figure 1)

The estimated mean baseline-adjusted FEV1 $AUEC_{0-6}$ for each individual dose of Albuterol Spiromax and ProAir HFA was significantly greater than that of placebo ($p<0.0001$ for all comparisons) (Table 4.25). Hence, all doses evaluated for each active product demonstrated significant bronchodilator efficacy relative to placebo.

The Sponsor also conducted an exploratory analysis to compare the estimated mean baseline-adjusted FEV1 $AUEC_{0-6}$ for each individual dose delivered by Albuterol Spiromax and ProAir HFA (Table 4.26). It seems that the results of two devices were comparable as the 90% CIs for treatment differences (Albuterol Spiromax - ProAir HFA) in baseline-adjusted FEV1 $AUEC_{0-6}$ included 0 at each dose level.

Table 4.25 Comparisons of Each Active Treatment with Placebo on Baseline-Adjusted FEV1 $AUEC_{0-6}$ (L·hr)

Treatment	N	Estimated Mean (SE) (L*hr)	95% CI	Model Results		
				Difference (SE) (Active – Placebo)	95% CI	P-value vs. Placebo
Albuterol *Spiromax* (90 mcg)	68	1.21 (0.224)	0.77, 1.66	0.97 (0.136)	0.70, 1.24	<0.0001
Albuterol *Spiromax* (180 mcg)	68	1.39 (0.224)	0.95, 1.84	1.15 (0.136)	0.88, 1.42	<0.0001
ProAir HFA (90 mcg)	70	1.12 (0.223)	0.68, 1.56	0.88 (0.136)	0.61, 1.15	<0.0001
ProAir HFA (180 mcg)	68	1.33 (0.224)	0.89, 1.77	1.08 (0.136)	0.81, 1.35	<0.0001
Placebo (0 mcg)	69	0.24 (0.224)	-0.20, 0.69	----------	----------	----------

(Source: CSR ABS-AS-201, page 63, Table 5)

Table 4.26 Comparisons of Baseline-Adjusted FEV1 $AUEC_{0-6}$ between Albuterol Spiromax and ProAir HFA at Each Active Dose Level

	90 mcg		180 mcg	
	Albuterol *Spiromax* N=68	*ProAir* HFA N=70	Albuterol *Spiromax* N=68	*ProAir* HFA N=68
Estimated Mean FEV_1 $AUEC_{0-6}$, L*hr (SE) [95% CI]	1.21 (0.224) [0.77, 1.66]	1.12 (0.223) [0.68, 1.56]	1.39 (0.224) [0.95, 1.84]	1.33 (0.224) [0.89, 1.77]
Albuterol *Spiromax* minus *ProAir* HFA (SE)	0.09 (0.136)		0.07 (0.136)	
90% CI	-0.13, 0.32		-0.16, 0.29	

(Source: CSR ABS-AS-201, page 64, Table 6)

The Sponsor also conducted an exploratory analysis to compare the estimated mean baseline-adjusted FEV1 $AUEC_{0-6}$ for two doses (90 µg and 180 µg) delivered by the same device (Table 4.27). It seems that there were no significant dose-response relationships as the 95% CIs for dose differences (180 µg - 90 µg) in baseline-adjusted FEV1 $AUEC_{0-6}$ included 0 for both devices.

Table 4.27 Comparisons of Baseline-Adjusted FEV1 $AUEC_{0-6}$ between 90 µg and 180 µg for Both Albuterol Spiromax and ProAir HFA

	Albuterol *Spiromax*		*ProAir* HFA	
	90 mcg N=68	180 mcg N=68	90 mcg N=70	180 mcg N=68
Estimated Mean FEV_1 $AUEC_{0-6}$, L*hr (SE) [95% CI]	1.21 (0.224) [0.77, 1.66]	1.39 (0.224) [0.95, 1.84]	1.12 (0.223) [0.68, 1.56]	1.33 (0.224) 0.89, 1.77]
180 mcg minus 90 mcg (SE)	0.18 (0.136)		0.20 (0.136)	
95% CI	-0.09, 0.45		-0.06, 0.47	
p-value	0.1884		0.1360	

(Source: CSR ABS-AS-201, page 68, Table 7)

Secondary endpoint

Following each single-dose, active treatment of albuterol inhalation, there was an overall increase in mean PPFEV1 at each 6-hour post-dose time point with peak mean PPFEV1 achieved approximately at 1 hour (Fig.4.14). The mean change from baseline PPFEV1 value was 1.53% for placebo and ranged from 9.45% to 11.8% for the active groups at 1 hour post-dose.

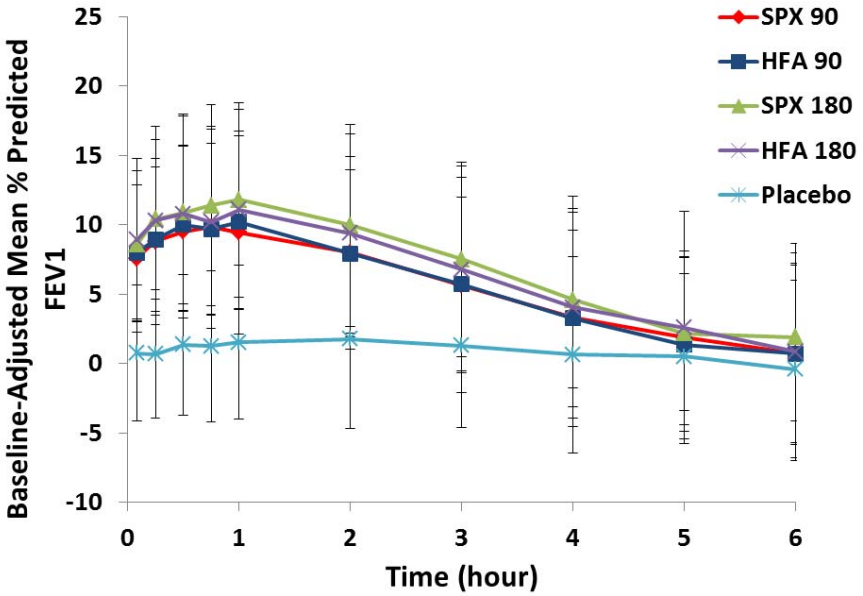

Fig.4.14 Arithmetic baseline-adjusted mean PPFEV1 following single-dose albuterol delivered as Albuterol Spiromax 90 µg (SPX90, red), Albuterol Spiromax 180 µg (SPX180, green), ProAir HFA 90 µg (HFA90, blue), ProAir HFA 180 µg (HFA180, purple), and placebo (P, cyan), respectively. Error bars represent the standard deviation. (Source: adapted from CSR ABS-AS-102 page 69, Figure 5)

The estimated mean baseline-adjusted PPFEV1 $AUEC_{0-6}$ for each individual dose of Albuterol Spiromax and ProAir HFA was significantly greater than that of placebo ($p<0.0001$ for all comparisons) (Table 4.28).

Table 4.28 Comparisons of Each Active Treatment with Placebo on Baseline-Adjusted PPFEV1 $AUEC_{0-6}$ (%·hr)

Treatment	N	Estimated Mean (SE) (%*hr)	95% CI	Model Results		
				Difference (SE) (Active – Placebo)	95% CI	P-value vs. Placebo
Albuterol *Spiromax* (90 mcg)	68	35.31 (4.497)	26.46, 44.17	27.73 (3.686)	20.47, 34.99	<0.0001
Albuterol *Spiromax* (180 mcg)	68	41.05 (4.495)	32.20, 49.90	33.47 (3.690)	26.21, 40.74	<0.0001
ProAir HFA (90 mcg)	70	33.19 (4.461)	24.41, 41.97	25.61 (3.680)	18.36, 32.85	<0.0001
ProAir HFA (180 mcg)	68	40.68 (4.496)	31.82, 49.53	33.10 (3.686)	25.84, 40.35	<0.0001
Placebo (0 mcg)	69	7.58 (4.482)	-1.25, 16.40	----------	----------	----------

(Source: CSR ABS-AS-201, page 70, Table 8)

!

The Sponsor also conducted an exploratory analysis to compare the estimated mean baseline-adjusted PPFEV1 $AUEC_{0-6}$ for each individual dose delivered by Albuterol Spiromax and ProAir HFA (Table 4.29). It seems that the results of two devices were comparable as the 90% CIs for treatment differences (Albuterol Spiromax - ProAir HFA) in baseline-adjusted FEV1 $AUEC_{0-6}$ included 0 at each dose level.

Table 4.29 Comparisons of Baseline-Adjusted PPFEV1 $AUEC_{0-6}$ between Albuterol Spiromax and ProAir HFA at Each Active Dose Level

	90 mcg		180 mcg	
	Albuterol *Spiromax* N=68	*ProAir* HFA N=70	Albuterol *Spiromax* N=68	*ProAir* HFA N=68
Estimated Mean Percent-Predicted FEV_1 $AUEC_{0-6}$, %*hr (SE) [95% CI]	35.31 (4.497) [26.46, 44.17]	33.19 (4.461) [24.41, 41.97]	41.05 (4.495) [32.20, 49.90]	40.68 (4.496) [31.82, 49.53]
Albuterol *Spiromax* minus *ProAir* HFA, %*hr (SE)	2.12 (3.684)		0.38 (3.692)	
90% CI	-3.96, 8.20		-5.72, 6.47	

!

(Source: CSR ABS-AS-201, page 71, Table 9)

!

The Sponsor also conducted an exploratory analysis to compare the estimated mean baseline-adjusted PPFEV1 $AUEC_{0-6}$ for two doses (90 µg and 180 µg) delivered by the same device (Table 4.30). The

differences between doses (180 µg - 90 µg) were 5.74 %·hr (p=0.121) for Albuterol Spiromax and 7.49 %·hr (p=0.043) for ProAir HFA.

Table 4.30 Comparisons of Baseline-Adjusted PPFEV1 $AUEC_{0-6}$ between 90 µg and 180 µg for Both Albuterol Spiromax and ProAir HFA

!

	Albuterol *Spiromax*		*ProAir* HFA	
	90 mcg N=68	**180 mcg N=68**	**90 mcg N=70**	**180 mcg N=68**
Estimated Mean Percent-Predicted FEV_1 $AUEC_{0-6}$ (SE) [95% CI]	35.31 (4.497) [26.46, 44.17]	41.05 (4.495) [32.20, 49.90]	33.19 (4.461) [24.41, 41.97]	40.68 (4.496) 31.82, 49.53]
180 mcg minus 90 mcg (SE)	5.74 (3.694)		7.49 (3.683)	
95% CI	-1.53, 13.01		0.24, 14.74	
p-value	0.1214		0.0430	

!

(Source: CSR ABS-AS-201, page 75, Table 10)

Other endpoints

1. The mean baseline-adjusted maximum FEV1 (L) over 6 hours post-dose of each active treatment (0.40 to 0.45 L) was significantly greater than that of the placebo (0.17 L) (Table 4.31 and Fig.4.15, p<0.0001). When the active treatments were compared between two devices at each of the dose levels, or two doses via each of the devices, the values were comparable (90% CI included 0).

Table 4.31 Comparison between Each Active Group and Placebo of Mean Baseline-Adjusted Maximum FEV1 Over 6 Hours (L)

Treatment	N	Maximal FEV1 (L)*	Difference from Placebo#	p Value
Albuterol Spiromax (90 µg)	68	0.40 (0.32, 0.48)	0.23 (0.18,0.28)	< 0.0001
Albuterol Spiromax (180 µg)	68	0.45 (0.37, 0.53)	0.28 (0.23,0.32)	< 0.0001
ProAir HFA (90 µg)	70	0.40 (0.32, 0.48)	0.23 (0.18,0.28)	< 0.0001
ProAir HFA (180 µg)	68	0.44 (0.36, 0.52)	0.26 (0.22,0.31)	< 0.0001
Placebo	69	0.17 (0.09, 0.25)		

*** Estimated mean baseline-adjusted maximal FEV1 (95% CI)**
 # Mean difference (95% CI)
Means, standard errors, confidence intervals, and p-values derived from a linear mixed model with fixed treatment, sequence, period, pooled center, baseline FEV1 as a covariate, and a random effect of subject.
(Source: adapted from CSR ABS-AS-201, page 171, Table 14.2.4.1)

2. The mean baseline-adjusted maximum percent-predicted FEV1 (maxPPFEV1, %) over 6 hours post-dose of each active treatment (12.0% to 13.1%) was significantly greater than that of the placebo (5.2%) (Table 4.32 and Fig.4.15, p<0.0001). When the active treatments were compared between two devices at each of the dose levels, or two doses via each of the devices, the values were comparable (90% CI included 0).

Table 4.32 Comparison between Each Active Group and Placebo of Mean Baseline-Adjusted Maximum PPFEV1 Over 6 Hours (%)

Treatment	N	Maximal PPFEV1 (%)*	Difference from Placebo#	p Value
Spiromax (90 µg)	68	11.98 (10.51, 13.45)	6.76 (5.44, 8.07)	< 0.0001
Spiromax (180 µg)	68	13.28 (11.81, 14.75)	8.06 (6.74, 9.37)	< 0.0001
ProAir HFA (90 µg)	70	12.02 (10.56, 13.48)	6.80 (5.49,8.11)	< 0.0001
ProAir HFA (180 µg)	68	13.13 (11.66, 14.60)	7.91 (6.59, 9.22)	< 0.0001
Placebo	69	5.22 (3.76, 6.68)		

*** Estimated mean baseline-adjusted maximal PPFEV1 (95% CI)**
 # Mean difference (95% CI)
Means, standard errors, confidence intervals, and p-values derived from a linear mixed model with fixed treatment, sequence, period, pooled center, baseline PPFEV1 as a covariate, and a random effect of subject. (Source: adapted from CSR ABS-AS-201, page 175, Table 14.2.5.1)

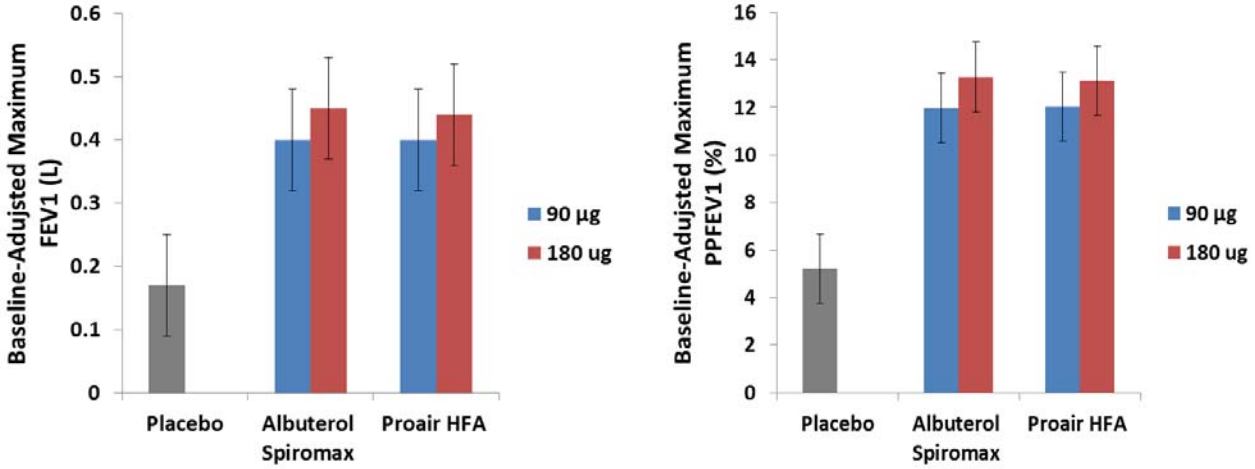

Fig.4.15 Estimated mean baseline-adjusted maximum FEV1 (left) and PPFEV1 (right) over 6-hour post-dose following treatment of placebo, Albuterol Spiromax (90 µg or 180 µg), or ProAir HFA (90 µg or 180 µg). Error bars represent 95% CIs. (Source: Table 4.31 and 4.32)

3. The time to response onset (the first time that an increase from baseline in FEV1 of at least 15% within 30 minutes post-dose)

   The percentage of subjects achieving at least a 15% increase in FEV1 from baseline was greater ($p<0.0001$) in all active treatment groups (44% to 63%) compared with placebo (3%) (Table 4.33).

Table 4.33 Number of Subjects with at Least 15% Increase from Baseline in FEV1 Within the First 30 Minutes by Treatment Group

Treatment	Subject Number	Responder Number (%)	p Value*
Albuterol Spiromax (90 µg)	68	30 (44.1%)	< 0.0001
Albuterol Spiromax (180 µg)	68	43 (63.2%)	< 0.0001
ProAir HFA (90 µg)	70	36 (51.4%)	< 0.0001
ProAir HFA (180 µg)	68	35 (51.5%)	< 0.0001
Placebo	69	2 (2.9%)	

*** p-values for comparison to Placebo are derived from a Mixed Logistic model with fixed effect period and treatment, with subject as random.**
(Source: adapted from CSR ABS-AS-201, page 179, Table 14.2.6.1)

The median times to a 15% or greater increase from baseline FEV1 of all 4 active treatments were the same (6 minutes with range of 3 to 30 minutes) (Table 4.34).

Table 4.34 First Time to 15% increase from Baseline in FEV1 for Responders

Treatment	Responder Number	First Time to 15% Increase of FEV1 (min)		
		Median	Minimum	Maximum
Albuterol Spiromax (90 µg)	30	6	3	30
Albuterol Spiromax (180 µg)	43	6	3	30
ProAir HFA (90 µg)	36	6	3	30
ProAir HFA (180 µg)	35	6	3	30
Placebo	2	15	4	26

(Source: adapted from CSR ABS-AS-201, page 181, Table 14.2.6.3)

4. The time to response onset (the first time that an increase from baseline in FEV1 of at least 12% within 30 minutes post-dose)

   The percentage of subjects achieving at least a 12% increase in FEV1 from baseline was greater ($p<0.0001$) in all active treatment groups (60% to 75%) compared with placebo (6%) (Table 4.35).

Table 4.35 Number of Subjects with at Least 12% Increase from Baseline in FEV1 Within the First 30 Minutes by Treatment Group

Treatment	Subject Number	Responder Number (%)	p Value*
Albuterol Spiromax (90 µg)	68	41 (60.3%)	< 0.0001
Albuterol Spiromax (180 µg)	68	48 (70.6%)	< 0.0001
ProAir HFA (90 µg)	70	48 (68.6%)	< 0.0001
ProAir HFA (180 µg)	68	51 (75.0%)	< 0.0001
Placebo	69	4 (5.8%)	

*** p-values for comparison to Placebo are derived from a Mixed Logistic model with fixed effect period and treatment, with subject as random.**
(Source: adapted from CSR ABS-AS-201, page 180, Table 14.2.6.2)

The median times to a 12% or greater increase from baseline FEV1 of all 4 active treatments were the same (6 minutes with range of 3 to 30 minutes) (Table 4.36).

Table 4.36 First Time to 12% increase from Baseline in FEV1 for Responders

Treatment	Responder N	First Time to 12% Increase of FEV1 (min)		
		Median	Minimum	Maximum
Albuterol Spiromax (90 µg)	41	6	3	29
Albuterol Spiromax (180 µg)	48	6	3	30
ProAir HFA (90 µg)	48	6	3	27
ProAir HFA (180 µg)	51	6	3	28
Placebo	4	18.5	4	30

(Source: adapted from CSR ABS-AS-201, page 182, Table 14.2.6.4)

5. The median time to maximum FEV1 was approximately 45 minutes post-dose for all active treatments (Table 4.37). The median time to maximum FEV1 for placebo was 64 minutes post-dose.

Table 4.37 Time to Maximum FEV1 for Different Treatments

Treatment	Subject N	Time to Maximum FEV1 (min)		
		Median	Minimum	Maximum
Albuterol Spiromax (90 µg)	68	44.5	4	356
Albuterol Spiromax (180 µg)	68	46.5	5	361
ProAir HFA (90 µg)	70	44.5	3	299
ProAir HFA (180 µg)	68	43.5	3	238
Placebo	69	64	3	360

(Source: adapted from CSR ABS-AS-201, page 183, Table 14.2.6.5)

6. The duration of 15% effect was defined as the time (in hours) from onset of a 15% or greater increase in FEV1 to offset of the 15% increase in FEV1 for subjects who responded within 30 minutes of treatment. The mean durations of the 15% or greater increase from baseline FEV1 were around 3 hours for all the active treatments (Table 4.38).

Table 4.38 Time (hours) of Duration of 15% Increase in FEV1 for Responders

Treatment	Responder N#	Duration of 15% increase in FEV1 (hr)*
Albuterol Spiromax (90 µg)	28	3.2 (1.75)
Albuterol Spiromax (180 µg)	38	3.1 (1.71)
ProAir HFA (90 µg)	33	2.8 (1.69)
ProAir HFA (180 µg)	32	3.0 (1.59)
Placebo	1	2.5

*** mean (SD)**
 # The numbers of responders were less than the numbers listed in Table 4.31 and Table 4.32. That's because the durations of some responders were not available due to non-consecutive FEV1 values above 15%.
(Source: adapted from CSR ABS-AS-201, page 184, Table 14.2.6.6)

7. The duration of 12% effect was defined as the time (in hours) from onset of a 12% or greater increase in FEV1 to offset of the 12% increase in FEV1 for subjects who responded within 30 minutes of treatment. The mean durations of the 12% or greater increase from baseline FEV1 were around 3 hours for all the active treatments (Table 4.39).

Table 4.39 Time (hours) of Duration of 12% Increase in FEV1 for Responders

Treatment	Responder N#	Duration of 12% increase in FEV1 (hr)*
Albuterol Spiromax (90 µg)	35	2.9 (1.98)
Albuterol Spiromax (180 µg)	39	3.3 (1.56)
ProAir HFA (90 µg)	45	2.7 (1.88)
ProAir HFA (180 µg)	48	2.7 (1.98)
Placebo	3	2.2 (1.78)

*** mean (SD)**
 # The numbers of responders were less than the numbers listed in Table 4.33 and Table 4.34. That's because the durations of some responders were not available due to non-consecutive FEV1 values above 15%.

(Source: adapted from CSR ABS-AS-201, page 185, Table 14.2.6.7)

PD/Vital Signs Results:

The maximum change from baseline in systolic blood pressure

The systolic blood pressure generally increased following all 5 treatments. The mean maximum increases from baseline for 4 active treatments (ranged from 6.7 to 8.6 mmHg) were similar to placebo (7.6 mmHg) (Table 4.40). The estimated mean maximal changes and weighted mean changes were 1.79 (90% CI = 0.11, 3.47) mmHg and 1.90 (90% CI = 0.56, 3.24) mmHg higher in Albuterol Spiromax group than ProAir HFA group at 90 µg dose level (Table 4.43 and Table 4.44). These differences between two devices appeared small and might not have clinical relevant meanings.

Table 4.40 Maximum Changes from Baseline in Systolic Blood Pressure Over 6 Hours Post-Dose by Treatment

Treatment	Subject N	Maximal Change from Baseline in Systolic Blood Pressure (mmHg)*
Albuterol Spiromax (90 µg)	68	7.7 (8.40)
Albuterol Spiromax (180 µg)	68	7.0 (8.23)
ProAir HFA (90 µg)	70	6.7 (7.58)
ProAir HFA (180 µg)	68	8.6 (7.85)
Placebo	69	7.6 (8.11)

*** mean (SD)**

(Source: adapted from CSR ABS-AS-201, page 207, Table 14.3.4.9)

The minimum change from baseline in diastolic blood pressure

The diastolic blood pressure generally decreased following all 5 treatments. The minimum changes from baseline for all 4 active treatments (ranged from -6.3 to -7.3 mmHg) were similar to placebo (-5.1 mmHg) (Table 4.41). The estimated mean minimum changes and weighted mean changes (Albuterol Spiromax - ProAir HFA) were 1.45 (90% CI = 0.22, 2.68) mmHg and 1.19 (90% CI = 0.34, 2.05) mmHg at 90 µg dose level (Table 4.43 and Table 4.44). Generally the differences between two devices were small and might not have clinical relevant meanings.

Table 4.41 Minimum Changes from Baseline in Diastolic Blood Pressure Over 6 Hours Post-Dose by Treatment

Treatment	Subject N	Minimum Changes from Baseline in Diastolic Blood Pressure (mmHg)*
Albuterol Spiromax (90 µg)	68	-6.8 (5.77)
Albuterol Spiromax (180 µg)	68	-6.9 (6.87)
ProAir HFA (90 µg)	70	-7.3 (6.27)
ProAir HFA (180 µg)	68	-6.3 (6.41)
Placebo	69	-5.1 (6.33)

*** mean (SD)**

(Source: adapted from CSR ABS-AS-201, page 208, Table 14.3.4.10)

The maximum change from baseline in heart rate

The heart rate generally increased following all 5 treatments. The mean maximum changes from baseline for all 4 active treatments (ranged from 6.9 to 8.0 bpm) were similar to placebo (7.5 bpm)

(Table 4.42). A statistical analysis of mean maximum changes and weighted mean changes from baseline in heart rate were comparable between devices, at both dose levels (Table 4.43 and Table 4.44).

Table 4.42 Maximum Changes from Baseline in Heart Rate Over 6 Hours Post-Dose by Treatment

Treatment	Subject N	Maximal Changes from Baseline in Diastolic Hear Rate (bpm)
Albuterol Spiromax (90 µg)	68	6.9 (7.6)
Albuterol Spiromax (180 µg)	68	7.1 (9.1)
ProAir HFA (90 µg)	70	7.3 (8.2)
ProAir HFA (180 µg)	68	8.0 (7.4)
Placebo	69	7.5 (7.2)

*** mean (SD)**
(Source: adapted from CSR ABS-AS-201, page 209, Table 14.3.4.11)

Table 4.43 Estimated Mean Maximum Changes from Baseline in Vital Signs Over 6 Hours Post-Dose by Treatment

	90 ug			180 ug		
	Albuterol Spiromax (T)*	ProAir HFA (R)*	Difference (90% CI) (T-R)	Albuterol Spiromax (T)*	ProAir HFA (R)*	Difference (90% CI) (T-R)
Systolic Blood Pressure (mmHg)	7.89 (0.916)	6.10 (0.907)	1.79 (0.11, 3.47)#	7.51 (0.917)	8.15 (0.917)	-0.64 (-2.33, 1.05)
Diastolic Blood Pressure (mmHg)	-6.04 (0.664)	-7.49 (0.666)	1.45 (0.22, 2.68)#	-6.72 (0.663)	-6.71 (0.663)	0.00 (-1.24, 1.23)
Heart Rate (bpm)	6.30 (0.852)	7.39 (0.842)	-1.09 (-2.51, 0.33)	6.86 (0.852)	7.28 (0.852)	-0.43 (-1.86, 1.00)

*** Estimated mean (SE)**
 # 90% CI did not include 0
Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and pooled center, baseline vital signs as a covariate, and a random effect for subject.
(Source: adapted from CSR ABS-AS-201, page 90, Table 17; page 91, Table 18; page 92, Table 19)

Table 4.44 Estimated Weighted Mean Changes from Baseline in Vital Signs Over 6 Hours Post-Dose by Treatment

	90 ug			180 ug		
	Albuterol Spiromax (T)*	ProAir HFA*	Difference (90% CI) (T-R)	Albuterol Spiromax (T)*	ProAir HFA*	Difference (90% CI) (T-R)
Systolic Blood Pressure (mmHg)	1.44 (0.790)	-0.46 (0.783)	1.90 (0.56, 3.24)#	0.41 (0.791)	0.56 (0.791)	-0.14 (-1.49, 1.20)
Diastolic Blood Pressure (mmHg)	-0.10 (0.533)	-1.29 (0.526)	1.19 (0.34, 2.05)#	-0.93 (0.532)	-0.66 (0.532)	-0.27 (-1.13, 0.58)
Heart Rate (bpm)	0.29 (0.681)	0.67 (0.675)	-0.38 (-1.42, 0.65)	0.11 (0.681)	0.60 (0.682)	-0.49 (-1.53, 0.55)

*** Estimated mean (SE)**
 # 90% CI did not include 0
Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and pooled center, baseline vital signs as a covariate, and a random effect for subject.

(Source: adapted from CSR ABS-AS-201, page 202, Table 14.3.4.4; page 203, Table 14.3.4.5, page 204, Table 14.3.4.6)

Conclusions:

Efficacy:

Primary endpoint: Compared with an estimated mean FEV1 $AUEC_{0-6}$ of 0.24 L·hr for placebo, each of the four active treatments demonstrated significant ($p<0.0001$) bronchodilator efficacy with estimated mean FEV1 $AUEC_{0-6}$ ranged from 1.12 to 1.39 L·hr. As an exploratory analysis, FEV1 $AUEC_{0-6}$ of Albuterol Spiromax and ProAir HFA were comparable at each of the two dose levels (90 µg and 180 µg) with the 90% CIs including 0. For comparison between different doses, FEV1 $AUEC_{0-6}$ of 90 µg and 180 µg were comparable for each of the devices with the 95% CIs including 0, indicating there was no significant beneficial effect of higher dose (180 µg) over lower dose (90 µg).

!

Secondary endpoint: Compared with an estimated mean PPFEV1 $AUEC_{0-6}$ of 7.58% for placebo, each of the four active treatments demonstrated significant ($p<0.0001$) bronchodilator efficacy with estimated mean PPFEV1 $AUEC_{0-6}$ ranged from 33.19% to 41.05%. As an exploratory analysis, PPFEV1 $AUEC_{0-6}$ of Albuterol Spiromax and ProAir HFA were comparable at each of the two dose levels (90 µg and 180 µg) with the 90% CIs including 0. For comparison between different doses, FEV1 $AUEC_{0-6}$ of 180 µg was significantly better than that of 90 µg if delivered by ProAir HFA ($p=0.043$) whereas the results were comparable if delivered by Albuterol Spiromax ($p=0.121$).

!

Other endpoints: 60% to 75% of subjects receiving active treatment exhibited an increase from their baseline FEV1 of at least 12% within 30 minutes post-dose compared with 6% of subjects receiving placebo. The percentage of responders exhibiting an increase from the baseline FEV1 of at least 15% were 44% to 63% for those receiving active treatment compared with 3% for subjects receiving placebo. Among responders, the median times to response were 3 minutes for all the active treatments by both criteria. The median times to maximal FEV1 over 6-hour post-dose period were similar (ranged from 43.5 minutes to 46.5 minutes) for all the active treatments. The durations of the response were similar (ranged from 2.7 hours to 3.3 hours) for all the active treatments by both criteria.

Safety:

Values of changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure and heart rate) appeared similar to placebo for both Albuterol Spiromax and ProAir HFA at both dose levels. Although comparisons showed statistical difference (90% CIs did not include 0) between Albuterol Spiromax and ProAir HFA at 90 µg dose level in systolic and diastolic blood pressures, generally the differences were numerically small and might not have clinical relevant meanings. In addition, the results demonstrated these differences had the same trend in both systolic and diastolic blood pressures.

Reviewer's comments:

According to the pre-defined objectives and primary endpoints, the efficacy was superior to placebo for both devices (Albuterol Spiromax and ProAir HFA) at both dose levels (90 µg and 180 µg). The exploratory statistical analysis exhibited that the efficacy was similar between two products at both dose levels. In addition, the median time (3 minutes) to response, the median time (around 45 minutes) to maximal FEV1, and the average duration of response (around 3 hours) were similar between two devices at both dose levels.

The dose-response relationship was only observed for ProAir HFA in secondary endpoint PPFEV1 $AUEC_{0-6}$. The Sponsor stated that the study was not powered to evaluate the dose-response relationship. However it's not clear why the Sponsor used 90% CIs to evaluate the efficacy difference between two devices whereas 95% CIs to evaluate dose-response relationship for each device.

4.1.4 Study ABS-AS-304

Study Type: Phase 3 efficacy, safety and steady-state PK study in asthma patients

Title: 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

Objective:
The primary objective of this study was to evaluate the efficacy of Albuterol MDPI relative to placebo, when administered for 12 weeks to subjects with persistent asthma who were on a stable dose of inhaled corticosteroids.

The secondary objective of this study was to evaluate the safety and tolerability of inhaled Albuterol MDPI and, in a subset of patients, to assess the pharmacokinetic profile of inhaled Albuterol MDPI following the first dose and at steady-state following 1 week of chronic dosing.

Study Design and Method:
This investigation was a 12-week, multicenter, randomized, double-blind, placebo-controlled, repeat-dose, parallel-group study to evaluate the efficacy and safety of Albuterol MDPI relative to Placebo MDPI in male and female subjects (ages 12 and older) with persistent asthma. The follow-up period was 7 ± 2 days. Total 160 patients at 29 centers in the US were randomized with 85 patients assigned to placebo MDPI and 75 patients assigned to Albuterol MDPI. 7 (8%) and 6 (8%) patients withdrew from placebo group and Albuterol MDPI group, respectively. A subset of 15 patients from placebo MDPI group and16 patients from Albuterol MDPI group participated PK sub-study.

The dosing regimen of two treatments was 2 inhalations (90 μg albuterol per inhalation for Albuterol MDPI) 4 times a day (QID) at approximately 7:00 AM, 12:00 PM, 5:00 PM and bedtime. The treatment period was 12 weeks.

Single-dose and steady-state PK profiles were evaluated at treatment day 1 and treatment day 8 ± 2, respectively. For single-dose profile, PK samples were collected at pre-dose (within 30 minutes prior to dosing), 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 10 hours post-dose. For steady-state profile, PK samples were collected at pre-dose (within 30 minutes prior to dosing), 0.25, 0.5, 1, 2, 3, 4 and 6 hours post-dose. Approximately 6 ml blood was required for each sample.!PK data from!15 patients from placebo MDPI group were excluded from PK analysis. For calculating PK parameters of albuterol, a BLQ value at time zero, at a sampling time before the first quantifiable plasma concentration, or at a sampling time between 2 quantifiable concentrations was treated as zero. All other BLQ values were treated as missing. PK parameters for albuterol were determined by non-compartmental method.

Primary Endpoints:
Efficacy:!!

- The primary efficacy endpoint was the baseline-adjusted FEV1 area under the time curve from time zero (pre-dose) up to 6 hr post-dose (FEV1 AUC_{0-6}, in L*hr) over the 12-week treatment period (computed on days 1, 8, and 85).

- The secondary efficacy endpoints were Baseline-adjusted FEV1 AUC_{0-6} at day 1, day 8 and day 85.

PK: AUC_{0-6}, C_{max}, T_{max}, terminal half-life $t_{1/2}$, AUC_{0-t} at single dose and estimated AUC_{0-24} at day 8

Bioanalytical Method:
Concentrations of albuterol were determined in human plasma samples using a validated HPLC-MS/MS with LLOQ at 2.00 pg/mL. The calibration curves of undiluted samples were linear over the range of concentrations from 2.00 to 1000.0 pg/mL albuterol. The intra batch (n=6) precision and accuracy were 4.44% (CV) and -5.00% (bias) at 6.00 pg/mL, respectively.

Demographics
Total 31(19%) adolescents were included in the study, though none of the adolescents participated in PK evaluation (Table 4.45). The mean body weight and BWI for 16 patients involved in PK study were 85.1 (SD=17.4) Kg and 28.4 (SD=3.98) Kg/m^2. 14 of 16 (88%) patients were overweight or obese.

Table 4.45 Subject Demographics

Demographic Variables	Placebo MDPI	Albuterol MDPI	Albuterol MDPI PK subset
Subject N	85	75	16
Mean Age (SD), years	36.7 (15.9)	40.0 (18.1)	45.1 (15.7)
Age Group, N (%)			
12 - 17 years	17 (20%)	14 (19%)	0 (0%)
18 - 64 years	67 (79%)	58 (77%)	15 (94%)
≥ 65 years	1 (1%)	3 (4%)	1 (6%)
Gender, N (%)			
Male	40 (47%)	39 (52%)	8 (50%)
Female	45 (53%)	36 (48%)	8 (50%)
Race, N (%)			
White	66 (78%)	59 (79%)	9 (56%)
Black	17 (20%)	11 (15%)	5 (31%)
Other	2 (2%)	5 (7%)	2 (13%)
Mean Body Weight (SD), Kg	79.8 (22.8)	79.6 (20.8)	85.1 (17.4)

(Source: adapted from CSR ABS-AS-304, page 74, Table 11)

PK Results:
It should be noted that quantifiable concentrations of albuterol were observed in 3 of the 16 predose plasma samples obtained from patients in the Albuterol MDPI treatment group at day 1, of which 2 had pre-dose concentrations >5% of their respective C_{max}. All of the analyses presented below included data from all active-treatment group patients.

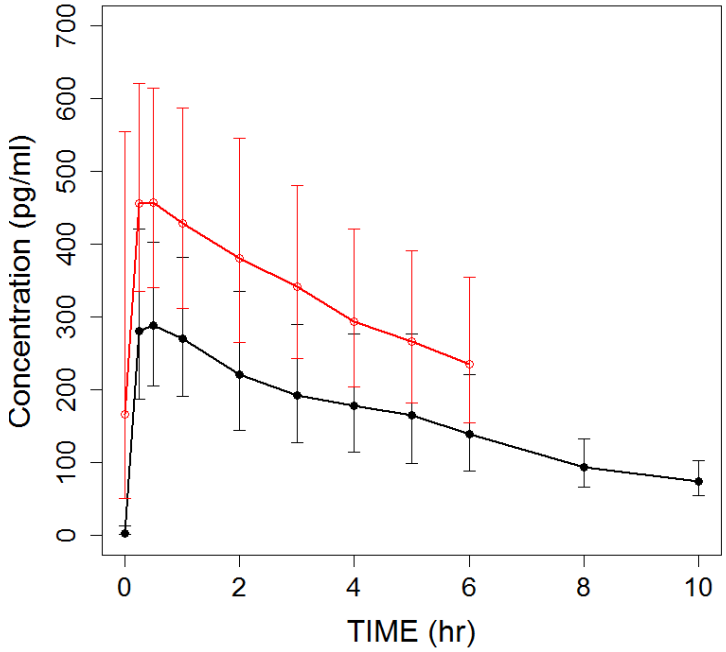

Fig.4.16 Geometric mean albuterol concentration-time profiles of albuterol following inhalation of 180 µg albuterol QID at day 1(black, N=16) or day 8 (red, N=16) via Albuterol MDPI. Error bars represent the standard deviation (concentration of BLQ at time 0 was set at 1/2 of the value of LLOQ). (Source: reviewer's analysis)

The single-dose and steady state concentration-time profiles of albuterol were shown in Fig.4.16. The summary of PK parameters was listed in Table 4.46.

Table 4.46 Geometric Mean (CV%) of Albuterol PK Parameters at Single-dose (day1) and Steady-state (day8) Following 180 µg QID Inhalation via Albuterol MDPI

PK Parameter	Day1 (Single-dose)	Day8
Subject N	16	16
AUC_{0-t} (pg·h/mL)*	1620 (39.1%)	2040 (35.7%)
AUC_{0-inf}/AUC_{τ} (pg·h/mL)**	2147 (35.5%)	2041 (35.2%)
C_{max} (pg/mL)	325 (37.6%)	479 (29.2%)
T_{max} (h)***	0.475 (0.18 - 4.95)	0.435 (0.25 - 2.02)
$T_{1/2}$ (h)	4.51 (33.7%)	5.51 (26.8%)

*** AUC_{0-10} for Day1 and AUC_{0-6} for Day8**
**** AUC_{0-inf} for Day1 and AUC_{τ} for day8**
***** Median (range)**
(Source: reviewer's analysis)

Following oral inhalation of single-dose 180 µg albuterol via Albuterol MDPI, systemic exposure as described by the geometric mean C_{max}, AUC_{0-10}, and AUC_{0-inf} values from 16 asthma patients, were 325 (CV = 38%) pg/mL, 1620 (CV = 39%) pg·hr/mL, and 2147 (CV = 36%) pg·hr/mL, respectively (Table 4.46). The median T_{max} was approximately 30 minutes post-dose. The geometric mean of terminal half-life was approximately 4.5 hours.

Following oral inhalation of 180 µg albuterol QID for 7 days, the steady state appeared reached as:

1) The geometric mean pre-dose concentration (219 pg/mL) was close to that of 6-hour post-dose (240 pg/mL) if patient ID 304_10259001 was excluded (reviewer's analysis, the pre-dose concentration of this patient was only 2.7 pg/ml, indicating a potential poor compliance).
2) The geometric mean ratio of $AUC_{\tau, \text{steady state}}$/ $AUC_{0\text{-inf, single dose}}$ was 0.95 (95% CI = 0.79, 1.15)

The systemic exposure as described by the geometric mean C_{max}, $AUC_{0\text{-}6}$, and AUC_{τ} values from 16 asthma patients, were 479 (CV = 29%) pg/mL, 2040 (CV = 36%) pg·hr/mL, and 2041 (CV = 35%) pg·hr/mL, respectively (Table 4.46). The median T_{max} was approximately 25 minutes post-dose. The geometric mean of accumulation factor as calculated from $AUC_{0\text{-}6, \text{steady state}}$/ $AUC_{0\text{-}6, \text{single dose}}$ ratio was 1.67 (95% CI = 1.33, 2.09). The geometric mean of accumulation factor as calculated from $C_{max,, \text{steady state}}$/ $C_{max, \text{single dose}}$ ratio was 1.48 (95% CI = 1.19, 1.83). The estimated geometric mean effective half-life was 4.8 (95%CI = 3.7, 6.4) hours if patient ID 304_10259001 was excluded (reviewer's analysis).

PK Conclusions:
After oral inhalation administration using Albuterol MDPI, albuterol was rapidly absorbed with a median T_{max} value of approximately 25 to 30 minutes. The geometric mean C_{max}, $AUC_{0\text{-}10}$, and $AUC_{0\text{-inf}}$ values from 16 asthma patients were 325 pg/mL, 1620 pg·hr/mL, and 2147 pg·hr/mL, respectively. The steady state was observed following QID administration for 7 days; the geometric mean of accumulation factor was 1.67. The geometric mean of terminal half-life was approximately 4.5 hours for single dose. The estimated geometric mean effective half-life was approximately 4.8 hours.

The efficacy and safety moiety of study ABS-AS-304 are reviewed by medical officer (Dr. Keith Hull) from DPARP.

Study ABS-AS-102

Note-
The Sponsor stated that two pediatric studies, study ABS-AS-102 (PK, PD and safety) and study ABS-AS-202 (Efficacy and safety), were completed at the time of submission of this NDA. However, only the study summaries were included in the package. Division of Clinical Pharmacology II reviewed the PK summary of study ABS-AS-102 in Module 2.7.2 (summary of clinical pharmacology studies), Section 2.2.3.

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

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

Objective:
The primary objective of this study was to compare the PK profiles of Albuterol MDPI and ProAir HFA after administration of a single inhaled dose of 180 µg albuterol base from each product in pediatric patients.

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

Study Design and Method:
This investigation was Phase 1, single-center, randomized, open-label, single-dose, 2-period, crossover study in pediatric patients aged 6 to 11 years, inclusive, with persistent asthma. Single dose of 180 µg albuterol (administered as 2 actuations of 90 µg albuterol) either from Albuterol MDPI or ProAir HFA

was orally inhaled during each treatment period. The washout period between two periods was 4 to 14 days. A total of 15 patients (5 males and 10 females) were enrolled with 14 were included in PK population; however, 13 patients were evaluable for PK in each treatment sequence.

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

PK Endpoints:
Primary: AUC_{0-t} and C_{max}
Secondary: AUC_{0-inf}, T_{max}, and $T_{1/2}$

PK Results:
The geometric mean AUC_{0-t} (measured up to 10 hours) of albuterol was comparable between two products with1663 (CV = 34%) pg·h/mL for Albuterol MDPI and 1651 (CV = 30%) for ProAir HFA after single-dose inhalation (Table 4.47). The geometric mean C_{max} of Albuterol MDPI was numerically higher than that of ProAir HFA, which is consistent with the results obtained from study ABS-AS-101. Results from a statistical comparison showed that the ratios (Albuterol MDPI/ProAir HFA) of AUC_{0-t} and C_{max} were 1.056 (90% CI = 0.880, 1.268) and 1.340 (90% CI = 1.098, 1.636), respectively.

Table 4.47 Geometric Mean (CV%) of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Adolescents

PK parameters	Albuterol MDPI	ProAir HFA
Patient N	13	13
AUC_{0-t} (pg·h/mL)	1663 (35%)	1651 (32%)
C_{max} (pg/mL)	353 (43%)	278 (35%)
AUC_{0-inf} (pg·h/mL)	1953 (32%)	2103 (25%)
T_{max} (hour)*	1.0 (0.5, 2.0)	2.0 (1.0, 2.0)
$T_{1/2}$ (hour)	3.5 (25%)	4.2 (28%)

*** median (range)**
(Source: adapted from Module 2.7.2 Summary of Clinical Pharmacology Studies, page 19, Table 4 and page 21, Table 5)

The median T_{max} of albuterol were 1.0 hour and 2.0 hour for Albuterol MDPI and ProAir HFA, respectively (Fig. 4.17). However the T_{max} may not be obtained as precisely as in study ABS-AS-304 as there was only one PK sample within 1 hour post-dose (30 minutes) in study ABS-AS-201.

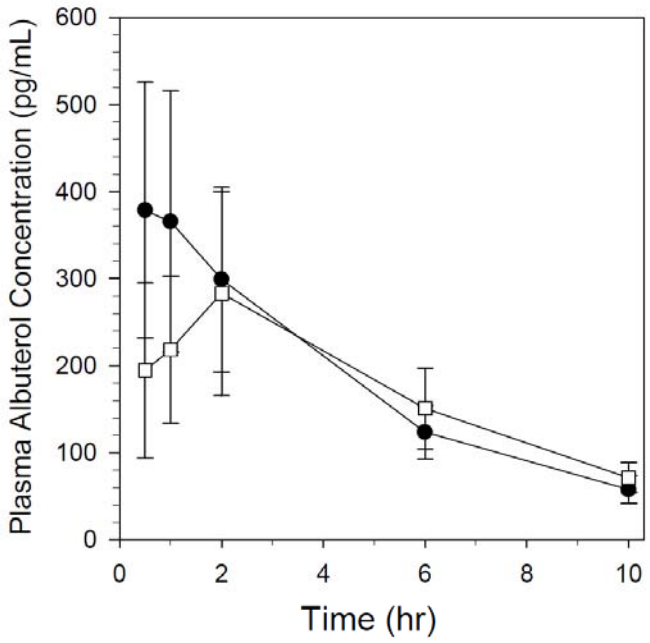

Fig.4.17 Mean plasma concentration-time profiles of albuterol following single-dose (180 µg) inhalation via Albuterol MDPI (solid circle) or ProAir HFA (open square). (Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, page 20, Figure 3)

Conclusions:
Following single-dose inhalation of 180 µg albuterol via Albuterol MDPI or ProAir HFA in children (6 to 11 years of age), AUC_{0-t} was equivalent between two products; Albuterol MDPI C_{max} was approximately 34% higher than that of ProAir HFA.

Albuterol systemic exposure following single-dose 180 µg inhalation via Albuterol MDPI was comparable between children (6 to 11 years of age, from study ABS-AS-201) and adults (from study ABS-AS-304) (Table 4.48).

Table 4.48 Geometric Mean (CV%) of Albuterol PK Parameters Following 180 µg Single-dose Inhalation in Children and Adults

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

*** median (range)**
(Source: Table 4.46 and 4.47)

4.2 Appendix – New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**21936**	**Brand Name**	**ProAir RespiClick**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Albuterol Sulfate**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Short-acting beta-adrenergic agonist**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	• **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.**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Multi-dose breath-actuated dry powder inhaler, 108 µg albuterol sulfate (90 µg albuterol base) per actuation**
Other discipline reviewers	**-**	**Dosing Regimen**	• **Treatment or prevention of bronchospasm in adults and adolescents age 12 and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient.** • **Prevention of exercise-induced bronchospasm in adults and adolescents age 12 and over: 2 inhalations 15 to 30 minutes before exercise.**
Date of Submission	**5/15/2014**	**Route of Administration**	**Inhalation**
Estimated Due Date of OCP Review	**3/15/2015**	**Sponsor**	**Teva Pharmaceutical Industries, Ltd.**
PDUFA Due Date	**5/15/2015**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			HPLC with tandem mass spectrometry
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -	**X**	**1**	**1**	Study ABS-AS-101
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	Study ABS-AS-201
multiple dose:	**X**	**3**	**3**	Study ABS-AS-101, ABS-AS-304, and IX-100-076
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**1**	**1**	Summary of study ABS-AS-102
geriatrics:				
renal impairment:				
hepatic impairment:				
PD/efficacy -				
Phase 2:	**X**	**2**	**2**	Study ABS-AS-201, and IX-100-076
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**	**1**	Study ABS-AS-101
Phase 3 clinical trial:				
Population Analyses -				
Meta-analysis:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**	**3**	Study ABS-AS-101, ABS-AS-201, and IX-100-076
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**5**	**5**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUNZHAO REN
01/27/2015

SATJIT S BRAR
01/27/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**21936**	**Brand Name**	**ProAir RespiClick**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Albuterol Sulfate**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Short-acting beta-adrenergic agonist**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	**• 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.**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Multi-dose breath-actuated dry powder inhaler, 108 µg albuterol sulfate (90 µg albuterol base) per actuation**
Other discipline reviewers	**-**	**Dosing Regimen**	**• Treatment or prevention of bronchospasm in adults and adolescents age 12 and older: 2 inhalations every 4 to 6 hours. In some patients, 1 inhalation every 4 hours may be sufficient. • Prevention of exercise-induced bronchospasm in adults and adolescents age 12 and over: 2 inhalations 15 to 30 minutes before exercise.**
Date of Submission	**5/15/2014**	**Route of Administration**	**Inhalation**
Estimated Due Date of OCP Review	**3/15/2015**	**Sponsor**	**Teva Pharmaceutical Industries, Ltd.**
PDUFA Due Date	**5/15/2015**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			HPLC with tandem mass spectrometry
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -	**X**	**1**	**1**	Study ABS-AS-101
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	Study ABS-AS-201

multiple dose:	**X**	**3**	**3**	Study ABS-AS-101, ABS-AS-304, and IX-100-076
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**1**	**1**	Summary of study ABS-AS-102
geriatrics:				
renal impairment:				
hepatic impairment:				
PD/efficacy -				
Phase 2:	**X**	**2**	**2**	Study ABS-AS-201, and IX-100-076
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**	**1**	Study ABS-AS-101
Phase 3 clinical trial:				
Population Analyses -				
Meta-analysis:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**	**3**	Study ABS-AS-101, ABS-AS-201, and IX-100-076
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**5**	**5**	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed product is the same product used in the pivotal clinical trials
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	Cross-reference to NDA21457
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	505(b)(2) pathway does not apply to bioavailability information for this NDA
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			

12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
13	Is the appropriate pharmacokinetic information submitted?	X			
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
17	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The pediatric studies reports are currently under preparation.
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
20	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes__

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

- None

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

- None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA OR SUPPLEMENT

Background

Albuterol is a short-acting beta2-adrenertic receptor agonist used as bronchodilator. Albuterol sulfate was first approved to treat asthma by FDA in 1981. Teva currently have three albuterol sulfate products with prescription status: NDA21457 Proair HFA® metered aerosol (approved in 2004), ANDA75343 inhalation solution (approved in 1999), and ANDA073419 oral syrup (approved in 1992). Teva initiated albuterol multi-dose dry powder inhaler (MDPI) program in 2009 under IND104532 and the proposed brand name was Albuterol Spiromax during IND stage because the inhalation device was Spiromax device from (b) (4)

Clinical Pharmacology Regulatory History

A pre-IND meeting was held on 3/27/2009. The Agency commented that:

1) Blood samples should be collected for pharmacokinetic (PK) assessment in some of the following studies to complete characterization of albuterol exposure of the proposed product (and the active comparator if there is one):
   - Single dose tolerability study in healthy subjects to assess acute bronchospasm;
   - Single-dose, dose-ranging, crossover, comparative efficacy and safety study in patients with asthma;
   - An escalating, comparative, cumulative dose pharmacodynamics (PD) 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 (I2 month) safety study to assess the safety of the new MDPI formulation and device performance.

2) The Agency agreed that the bioequivalence (between the proposed product and the active comparator) was not the goal for PK studies.

3) The Sponsor should wait to initiate the pediatric studies until data from the adult studies are available.

On 1/27/2010, IND104532 was safe to proceed. Liang Zhao, the clinical pharmacology reviewer, has no concerns regarding the study protocol (Protocol No. ABS-AS-101).

An end-of-Phase 2 meeting was held on 10/5/2010. The Agency commented that:

1) The Sponsor should consider obtaining first dose and steady state PK data at the proposed therapeutic dose in a subset of patients in one of the clinical studies for labeling purposes.

2) Based on Phase 1/2 safety, efficacy and PK results from adults, the Sponsor can initiate the pediatric Phase 1/2 PK studies without waiting for completion of the Phase 3 program in adults and adolescents.

A pre-NDA meeting was held on 11/19/2013. The Agency did not have any specific clinical pharmacology-related comments.

Device Modifications

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

1) (b) (4) was used for the first IVAX Spiromax studies ex-USA (IX-100-076 and IX-101-076; delivered 100 µg albuterol sulfate per actuation);

2) (b) (4) was used in the supportive studies ABS-AS-101, ABS-AS-201, (b) (4)

3) (b) (4) was used in the pivotal safety studies in asthma: ABS-AS-307, ABS-AS-301, and ABS-AS-304, and in the study in EIB, ABS-AS-302, and in study ABS-AS-308;

4) Two additional pediatric studies (ABS-AS-102 and ABS-AS-202) have been completed utilizing the (b) (4) device and clinical study reports are in preparation.

It seems there is no difference on the mechanical dry powder delivery system between (b) (4) and (b) (4) Compared to (b) (4) there are (b) (4)

Clinical Pharmacology Studies

The Sponsor submitted four clinical pharmacology study reports and one pediatric study summary in this NDA:

Study ID	Phase	subjects	Dose**	Comparator	Objectives
ABS-AS-101	1	45 asthma adults completed	cumulative dose of 1440 ug (cumulative 1, 2, 4, 8, 16 puffs, each dose 30 min apart)	ProAir HFA (90 µg/act), Placebo	PK/PD, efficacy, safety
ABS-AS-201	2	68 asthma adults and adolescents completed	single dose (90 r 180 µg)	ProAir HFA (90 µg/act), Placebo	Efficacy/PD, safety
ABS-AS-304	3	146 asthma adults and adolescents	180 µg QID, 12-week	Placebo	PK, efficacy, safety
IX-100·076*	2	59 asthma adults completed	cumulative dose of 800 µg (cumulative 1, 2, 4, 8 puffs, each dose 30 min apart)	Ventolin MDI (100 µg/act), Ventolin Diskhale (200 µg/act), Ventolin Accuhaler (200 µg/act), Placebo	Efficacy/PD, safety
ABS-AS-102 (summary)	1	15 children (4 to 11 years) completed	180 µg single-dose	ProAir HFA (100 µg/act)	PK/PD, safety

*** Study was conducted in South Africa by using early MDPI device (b) (4) with the by-then product name as Salbutamol-MDPI.**
**** Dose is defined as albuterol base does.**

The sponsor stated the following clinical pharmacology conclusions:

1) In study ABS-AS-101,
    - Efficacy: For the primary endpoint (baseline-adjusted FEV1 at 30 minutes after each of the five cumulative doses), each treatment produced robust increases in FEV1 over baseline at each cumulative dose level, and a dose response was observed for each product. The magnitude of the differences between MDPI and HFA was small (mean treatment differences of -0.07 to -0.03 L), with each 90% CI being entirely contained within the pre-defined limits of ± 0.20 L.

    - PK: The geometric mean treatment ratios (MDPI/HFA) for AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively. The systemic exposure following MDPI high cumulative-dose administration (1440 µg of albuterol) was comparable with that of HFA Inhalation Aerosol based on the AUC_{0-t} analyses.

    - PD: Changes in the PD measures (serial plasma glucose and potassium concentrations, QTc intervals from serial ECGs, and serial heart rate, systolic blood pressure, and diastolic blood pressure) of MDPI were generally comparable to those of HFA.

2) In study ABS-AS-201, baseline FEV1 values were similar for each of the 5 treatment arms, ranging from 2.15 to 2.17 L. The estimated mean FEV1 $AUEC_{0-6}$ for each individual dose of MDPI and HFA was significantly greater than the estimated mean FEV1 $AUEC_{0-6}$ for placebo ($p<0.0001$ for all comparisons). Treatment differences (MDPI - HFA) were 0.09 L*hr (SE=0.136, 90% CI= -0.13, 0.32) for the 90 µg dose and 0.07 L*hr (SE=0.136, 90% CI= -0.16, 0.29) for the 180 µg dose.

3) In study ABS-AS-304, albuterol was rapidly absorbed into the systemic circulation (T_{max} were 0.48 hour and 0.44 hour for single- or multiple-dose, respectively). The accumulation observed (1.5-fold for C_{max} and 1.7-fold for AUC_{0-t}) following QID dosing for 1 week was as predicted by the single-dose results, demonstrating that the pharmacokinetic characteristics of albuterol under these study conditions were time-independent.

4) In study IX-100-076, an early device (b) (4) was designed to deliver 100 µg albuterol sulfate per actuation. Equivalence was established between Salbutamol-MDPI and Ventolin®- MDI treatments with respect to FEV1 and PEF response at each dose level.

5) In study ABS-AS-102,

    - The geometric mean treatment ratios (MDPI/HFA) for AUC_{0-t} and C_{max} were 1.06 (90% CI = 0.88, 1.27) and 1.34 (90% CI = 1.10, 1.64), respectively. The T_{max} and $T_{1/2}$ were shorter for MDPI. The T_{max} were 1.01 hour and 1.77 hour for MDPI and

HFA, respectively. The $T_{1/2}$ was 3.6 hour and 4.3 hour for MDPI and HFA, respectively.

- Single dose MDPI and HFA resulted in comparable PD, as there were no notable differences between the 2 treatments on heart rate or blood pressure at any time point measured after administration of single doses. This comparable systemic PD is in line with comparable systemic pharmacokinetics.

Acceptance of these findings will be a review issue.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUNZHAO REN
06/09/2014

SATJIT S BRAR
06/09/2014