



Dose-Ranging and Cumulative Dose Studies of Albuterol Sulfate MDI in Co-Suspension Delivery™ Technology (AS MDI; PT007) in Patients with Asthma: the ASPEN and ANTORA Trials

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Abstract

Background and Objectives Co-suspension Delivery™ Technology has been developed for the administration of albuterol sulfate pressurised inhalation suspension via metered-dose inhaler (AS MDI, PT007). We assessed the efficacy and safety of AS MDI versus Proventil® in order to determine the optimal dose of AS MDI to take to Phase III clinical trials.

Methods ASPEN (NCT03371459) and ANTORA (NCT03364608) were Phase II, randomised, crossover, multicentre studies of AS MDI versus Proventil® in patients with persistent asthma. In ASPEN, 46 patients received cumulative-dose treatments (90 µg/inhalation using 1 + 1 + 2 + 4 + 8 inhalations at 30-minute intervals) in 1 of 2 possible sequences: AS MDI/Proventil or Proventil/AS MDI. In ANTORA, 86 patients were randomised to one of 10 treatment sequences of AS MDI (90 µg or 180 µg), placebo MDI, or Proventil (90 µg or 180 µg). The primary endpoints were baseline-adjusted forced expiratory volume in 1 second (FEV₁) 30 minutes after each cumulative dose (ASPEN) and change from baseline in FEV₁ area under the curve from 0 to 6 h (ANTORA). Safety was assessed in both studies.

Results In ASPEN, AS MDI was equivalent to Proventil (within pre-specified bounds of ± 200 mL) following cumulative doses of albuterol up to 1440 µg for the primary endpoint. In ANTORA, 90 µg and 180 µg doses of AS MDI and Proventil were significantly superior to placebo MDI ($p < 0.0001$), and AS MDI was non-inferior to Proventil at both doses, based on a margin of 100 mL. No new safety concerns were identified.

Conclusion The effects of albuterol delivered via AS MDI and Proventil on bronchodilation were equivalent, supporting the selection of AS MDI 180 µg to be taken into Phase III clinical trials, either alone or in combination with an inhaled corticosteroid.

Trial Registration number ASPEN (NCT03371459); Date of registration: 29/12/2017. ANTORA (NCT03364608); Date of registration: 15/12/2017.

1 Introduction

Asthma is a heterogeneous inflammatory airway disease [1, 2] defined by a history of variable respiratory symptoms including wheeze and cough and with variable expiratory airflow obstruction [1, 2] across all asthma severities [1]. All patients are at risk of preventable and potentially serious exacerbations, irrespective of asthma severity.

Short-acting β_2 -agonists (SABAs), such as albuterol (salbutamol), have been prescribed worldwide for over 50 years, to provide quick relief of asthma symptoms as ‘rescue’ medication [1]. Albuterol can be combined with inhaled corticosteroids (ICS) or other anti-inflammatory medications to help patients receive an anti-inflammatory benefit each time they utilise a rescue inhaler. Combining rescue and anti-inflammatory therapies is now recommended for all asthma

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Key Points

The effects on lung function of albuterol sulfate delivered either via a novel co-suspension delivery technology pressurised metered-dose inhaler (AS MDI) or via the Proventil inhaler were equivalent at doses of albuterol up to 1440 µg.

At doses of 90 µg and 180 µg, AS MDI was more effective than placebo MDI and non-inferior to Proventil in improving lung function.

The data support the selection of AS MDI 180 µg to be taken into Phase III clinical trials.

patients in the most recent update of the Global Initiative for Asthma (GINA) guidelines [1].

An innovative Co-suspension Delivery™ Technology has been developed and utilised in several mono- and combination inhalation therapy products (e.g. Bevespi Aerosphere™, Breztri Aerosphere™), including albuterol sulfate (hereafter referred to as albuterol) pressurised inhalation suspension delivered via metered-dose inhaler (AS MDI, PT007). Micronised albuterol sulfate, a racemic salt of albuterol, is co-suspended with spray-dried porous particles (i.e., phospholipid, 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride) in a hydrofluoroalkane (HFA) propellant. These porous particles form strong, nonspecific associations with albuterol to enable consistent delivery of single or combination products with respirable particle sizes after each inhalation to potentially treat the entire lung.

Phase II studies were required to select the optimal dose of albuterol in AS MDI, which then determined the albuterol dose to use in subsequent SABA/ICS combination (PT027) Phase III studies (NCT03769090, NCT03847896). This paper details the results of two such Phase II trials in patients with persistent asthma: ASPEN (NCT03371459) and ANTORA (NCT03364608).

ASPEN was a cumulative-dose study investigating the efficacy and safety of cumulative doses up to 1440 µg of AS MDI versus Proventil® HFA, in addition to characterising its pharmacokinetic/relative systemic bioavailability and extrapulmonary pharmacodynamic properties in adults with persistent asthma.

ANTORA was a dose-ranging study comparing the bronchodilatory efficacy and safety of 90 µg and 180 µg doses of AS MDI versus a matching placebo MDI and open-label Proventil in adults and adolescents with persistent asthma. The objectives of ANTORA were (1) to confirm that the dose of albuterol from AS MDI delivered comparable efficacy relative to Proventil; and (2) to assess the safety and tolerability of AS MDI relative to Proventil and placebo.

2 Methods

2.1 Study Designs and Patients

Both ASPEN (PT007002; NCT03371459) and ANTORA (PT007001; NCT03364608) were Phase II, randomised, crossover, multicentre studies. ASPEN was an open-label, two-period, cumulative dose trial, whereas ANTORA was a single-dose, five-period, dose-ranging study. Both studies consisted of screening/run-in periods, followed by a sequence of treatment periods separated by 3- to 7-day washouts (Supplementary Figure S1). AS MDI and placebo were administered as blinded treatments and Proventil was administered as an open-label treatment.

Patients eligible for randomisation were aged between 18 and 45 years (ASPEN) or 12 and 65 years (ANTORA); had stable, physician-diagnosed persistent asthma for at least 6 months prior to screening; had previously been treated with as-needed SABA-alone, or with stable, low-to-medium dose ICS alone or in combination with a long-acting β_2 -agonist (LABA) for ≥ 30 days prior to screening; had pre-bronchodilator forced expiratory volume in 1 s (FEV₁) of $\geq 40\%$ and $< 90\%$ (ASPEN) and $\geq 50\%$ and $< 80\%$ (ANTORA) of predicted normal value; had reversibility of $\geq 15\%$ following albuterol (Ventolin®) administration; and had to be willing to come in for morning treatment visits, and to withhold caffeine for 6 h, rescue albuterol for at least 6 h (ANTORA), and rescue ipratropium for at least 8 h (ASPEN) prior to visits.

Exclusion criteria included a diagnosis of chronic obstructive pulmonary disease (COPD) or other significant lung disease; oral corticosteroid for any use ≤ 6 months prior to screening; current or former smoker with a history of > 10 pack-years, former smokers who had stopped smoking < 6 months before screening; hospitalisation due to asthma ≤ 6 months prior to screening; and historical or current evidence of a clinically significant disease including cardiovascular (e.g., congestive heart failure), hepatic, renal, haematological, neuropsychological, endocrine (e.g., uncontrolled diabetes mellitus), or gastrointestinal disease. Significant disease was defined as any that would have put the subject at risk during the study or one that could have affected the efficacy or safety endpoints, should the condition have worsened during the study.

After signing informed consent, patients receiving ICS (with or without LABA) prior to study entry were switched to budesonide (Pulmicort Flexhaler®) 180 µg one or two inhalations twice daily. At each visit, pulmonary function tests (PFTs) were used to assess bronchodilation activity. To reduce bias, dosing and spirometry assessments were performed separately so that medical staff conducting the spirometry assessments were blinded to the identity of the study treatment administered.

2.1.1 ASPEN

All patients were allowed to take sponsor-provided rescue medication; albuterol (Ventolin) 90 µg/inhalation as needed (only up to 48 h before Visit 2) and ipratropium bromide 17 µg/inhalation as needed (from 48 h before Visit 2 through the remainder of the study). Ipratropium bromide was used as rescue to ensure that it would not confound the measurement of albuterol pharmacokinetics.

Eligible patients were randomised to receive one of two treatment sequences, A/B or B/A, where A is AS MDI 90 µg and B is Proventil 90 µg. Subjects received five doses of AS MDI and Proventil during Visits 2 and 3 for a total cumulative dose of 1440 µg each; cumulative doses were given as 1 + 1 + 2 + 4 + 8 inhalations (doses given 30 minutes apart), equalling doses of 90, 90, 180, 360, and 720 µg, respectively.

Treatment periods were separated by a 3- to 7-day wash-out period, with a follow-up telephone assessment 3–7 days after the final treatment period.

2.1.2 ANTORA

The screening/run-in period in the ANTORA study was identical to that in the ASPEN study, except ipratropium was not administered prior to Visit 2. Throughout the study, all patients were allowed to take rescue medication in the form of sponsor-provided albuterol (Ventolin®) 90 µg/inhalation as needed (up to 6 h prior to each treatment visit).

Eligible patients were randomised to one of 10 possible treatment sequences, based on a standard Williams design [3], and received a single dose of treatment at each visit. Each treatment sequence comprised all five of the following treatments: AS MDI 90 µg (2 inhalations of 45 µg/inhalation); AS MDI 180 µg (2 inhalations of 90 µg/inhalation); placebo MDI (2 inhalations); Proventil 90 µg (1 inhalation of 90 µg/inhalation); Proventil 180 µg (2 inhalations of 90 µg/inhalation).

2.2 Study Endpoints

2.2.1 ASPEN

The primary efficacy endpoint of ASPEN was change from baseline in FEV₁ 30 minutes after each cumulative dose up to 1440 µg. Key secondary efficacy endpoints included change from baseline in FEV₁ area under the curve from 0 to 6 h (AUC₀₋₆) after the last cumulative dose; extrapulmonary pharmacodynamic parameters (change, maximum change, and time-weighted average change from baseline); pharmacokinetic properties (albuterol systemic bioavailability); and adverse events (AEs) and serious adverse events (SAEs). AEs were determined by the primary investigator at each site. An AE was defined as any unfavourable and

unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug. An SAE was defined as an AE resulting in death, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity to conduct normal life functions, or a congenital anomaly/birth defect.

Approximately 35 mL of blood per subject was collected during the study for clinical laboratory tests. Extrapulmonary pharmacodynamic parameters included Fridericia-corrected QT interval (QTcF), heart rate, serum glucose, serum potassium, diastolic blood pressure (DBP) and systolic blood pressure (SBP). They were all measured pre-dose, and at 12 times post-dose, at 15 minutes after each cumulative dose, and then at 30, 45, 60, 120, 180, 240 and 360 minutes after the final dose. For the pharmacokinetic analysis, blood samples to determine the plasma concentrations of albuterol were drawn during the treatment period at Visits 2 and 3 at the following time points: 30 minutes pre-dose, at 15 minutes after each cumulative dose, and then at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 minutes after the final dose. Approximately 220 mL of blood was collected at Visits 2 and 3 for subjects participating in the pharmacokinetic analysis (~255 mL of blood was collected in these subjects over the course of the study). Samples were collected, handled, labelled, stored, and shipped as detailed in the laboratory manual, and plasma samples were analysed for albuterol by a central laboratory according to standardised, validated assays. Albuterol systemic bioavailability parameters included plasma concentration 15 minutes after each cumulative dose (C_{15min}); area under the concentration-time curve from time 0 (pre-dose) to the time of the last measurable plasma concentration (AUC_{0-t}); and maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}). Further details on the pharmacokinetic parameters are provided in the Supplementary Material.

2.2.2 ANTORA

The primary efficacy endpoint of ANTORA was change from baseline in FEV₁ AUC₀₋₆. Secondary endpoints were change from baseline in FEV₁ AUC₀₋₄ and peak change from baseline in FEV₁. Other additional endpoints investigated included percentage of subjects achieving 12% improvement in FEV₁ from baseline within 30 minutes of dose (FEV₁% predicted > 12% is a well-recognised cut-off for determining a positive bronchodilator response [4, 5]), time to onset of this response, and safety, including AEs (defined the same as in ASPEN), laboratory parameters, vital signs, and electrocardiogram recordings. Approximately 10 mL of blood was collected per subject during the study for clinical laboratory tests.

2.3 Statistical Analyses

Data processing, descriptive reporting, and analysis of the efficacy, extrapulmonary pharmacodynamic, pharmacokinetic, and safety data were performed using SAS version 9.4. All efficacy and safety parameters were summarised by treatment. Categorical variables were summarised by treatment with frequency counts and percentages. Efficacy analyses in both studies were performed for the Modified Intent-to-Treat (mITT) analysis set (all patients who received study treatment and had post-treatment efficacy data at all treatment periods for ASPEN and at least two treatment periods for ANTORA). Pharmacokinetic and extrapulmonary pharmacodynamic analyses in ASPEN were performed for the Pharmacokinetic and Per Protocol Analysis Sets (all randomised patients who received ≥ 1 dose of the study drug for whom ≥ 1 primary pharmacokinetic parameter could be calculated, and all randomised patients who received ≥ 1 dose of the study drug and had post-treatment extrapulmonary pharmacodynamic data, respectively).

No formal analysis for safety was planned, and safety results were listed by treatment.

2.3.1 ASPEN

Change from baseline in FEV₁ after each cumulative dose was analysed using a linear mixed effects model with a random subject effect for the correlation across periods and an unstructured covariance matrix for the repeated measures within subject-periods. Fixed effects were as follows: treatment, cumulative dose level, treatment-by-cumulative dose interaction, and period as categorical covariates and baseline FEV₁ as a continuous covariate.

FEV₁ AUC₀₋₆ was defined as the AUC for the change from baseline in FEV₁ calculated using the trapezoidal rule for all subjects with at least 1 non-missing data point during the first 2 h post-dose. For AUC calculations, the value of the spirometry parameter at time 0 was the change from baseline in pre-bronchodilator FEV₁ at 30 minutes after the 4th cumulative dose (720 µg) at the visit. All AUC values were normalised for length of follow-up (typically 6 h). FEV₁ AUC₀₋₆ was also analysed using a linear mixed model with a random subject effect, with fixed effects of treatment and period as categorical covariates and baseline FEV₁ as a continuous covariate.

Equivalence was analysed by comparing the 90% confidence interval (CI) for the between-treatment differences after each cumulative dose with predefined bounds of ± 200 mL. This margin was selected based on precedence from a similarly designed cumulative-dose study comparing ProAir Respiclick versus ProAir HFA [6], from which a mean change from baseline in FEV₁ on the order of 700 mL was observed, thus the ± 200 mL cut-off accounts for greater

variability. FEV₁ AUC₀₋₆ after the last cumulative dose was analysed using a linear mixed-effects model with a random subject effect; fixed effects were treatment and period as categorical covariates and baseline FEV₁ as a continuous covariate.

Pharmacokinetic parameters were estimated by non-compartmental analysis using Phoenix[®] WinNonlin[®] Version 6.4. AUC_{0-t} and C_{max} values for albuterol were natural log-transformed and were each analysed with a linear mixed effects model containing fixed effects of treatment and period and a random effect of subject. Estimated geometric mean ratios with 90% CIs were provided.

Extrapulmonary pharmacodynamic parameters were analysed using a model similar to that described for the primary efficacy endpoint.

2.3.2 ANTORA

As in ASPEN, change from baseline in FEV₁ AUC₀₋₆ was analysed using a linear mixed model with a random subject effect, with fixed effects of treatment, treatment sequence, and period as categorical covariates and baseline FEV₁ as a continuous covariate.

FEV₁ area under the curve from 0 to 4 h (AUC₀₋₄) was calculated in a similar manner to FEV₁ AUC₀₋₆, with the trapezoidal rule implemented through the 4-h nominal time point and AUC values normalised accordingly. The largest FEV₁ value measured during the 6 h after dosing was used to calculate the peak change from baseline in FEV₁. An approach similar to that used for the primary endpoint was used to analyse the secondary endpoints (FEV₁ AUC₀₋₆ and peak change from baseline in FEV₁); linear mixed models with a random subject effect, with fixed effects of treatment, treatment sequence, baseline FEV₁, and period.

Superiority comparisons for the active formulations versus placebo were conducted using a dose-ordered approach in the following order (with subsequent comparisons performed only after detection of statistical significance for earlier comparisons): Proventil 180 µg versus placebo; AS MDI 180 µg versus placebo; Proventil 90 µg versus placebo; AS MDI 90 µg versus placebo.

If both AS MDI 180 µg and Proventil 180 µg were statistically superior to placebo MDI, the non-inferiority of AS MDI 180 µg versus Proventil 180 µg for FEV₁ AUC₀₋₆ was assessed as an exploratory endpoint using a non-inferiority margin of 100 mL. This margin was selected as the known minimal perceivable improvement for FEV₁ has been previously reported to be 230 mL [7, 8]. A 100 mL non-inferiority margin is appropriate for this magnitude of change and represents slightly less than half the minimal perceptible FEV₁ value. Secondary efficacy analyses also used linear mixed models with a random subject effect; fixed effects included treatment, treatment sequence, baseline FEV₁, and period.

Peak change from baseline in FEV₁ was calculated using the highest FEV₁ value measured during the 6 h after dosing.

3 Results

3.1 Patient Demographics

Of the 69 patients screened in ASPEN, 46 were randomised and received ≥ 1 dose of study treatment, with 45 completing both treatment periods (mITT analysis set). One patient was lost to follow-up (Table 1). Patients' mean age was 34.2 years (range 20–45), and just under half were female (48.9%). Patients had a mean pre-bronchodilator FEV₁ 63.6% predicted. Before screening, 42.2% and 51.1% of patients were receiving as-needed SABA alone and ICS/LABA, respectively, with the remainder treated with ICS (Table 2).

In ANTORA, 116 patients were screened, 86 were randomised and received ≥ 1 dose of study treatment, and 80 completed at least two treatment periods (mITT analysis set). A total of 78 patients completed all five treatment periods (Table 1). The mean age of patients was 42.6 years (range 13–64), and just over half were female (53.8%). Patients had a mean pre-bronchodilator FEV₁ 68.0% predicted. Prior to screening, patients were receiving as-needed SABA alone (55.0%), ICS/LABA (36.3%), or ICS (8.8%) (Table 2).

Per protocol, all patients demonstrated at least 15% reversibility to albuterol (Ventolin) during screening. The mean reversibility post-albuterol in ASPEN and ANTORA was 29.3% (standard deviation [SD] 13.1%) and 25.8% (SD 10.6%), and the median reversibility was 23.7% and 22.0%, respectively. Full patient baseline demographics for both trials are presented in Table 2.

3.2 ASPEN

3.2.1 Efficacy Results

Cumulative doses of both AS MDI and Proventil were associated with increases in the least squares (LS) mean change from baseline in FEV₁ (30 minutes after each dose), peaking at approximately 2.5 h post-administration of the first cumulative dose (Fig. 1). AS MDI was equivalent to Proventil for the LS mean change from baseline in FEV₁ after each cumulative dose, as the 90% CIs for the treatment differences were contained within the pre-specified bounds of ± 200 mL (Table 3).

AS MDI and Proventil were equivalent for the change from baseline in FEV₁ AUC_{0–6} after the last cumulative dose, with LS mean improvements of 561 mL (95% CI

Table 1 Randomisation of patients to treatment in ASPEN and ANTORA studies

Category	ASPEN (N=69) n (%)	ANTORA (N=116) n (%)
Not randomised ^a	23 (33.3)	30 (25.9)
Randomised ^a	46 (66.7)	86 (74.1)
Not treated ^b	0	0
Treated ^b	46 (100.0)	86 (100)
With AS MDI	45 (97.8)	–
AS MDI 90 µg	–	81 (94.2)
AS MDI 180 µg	–	81 (94.2)
With Proventil [®]	46 (100.0)	–
Proventil 90 µg	–	82 (95.3)
Proventil 180 µg	–	79 (91.9)
With placebo	N/A	82 (95.3)
Completed study ^b	45 (97.8)	78 (90.7)
Premature discontinuation ^b	1 (2.2)	8 (9.3)

^a% = $100 \times n/N$, where n = number of subjects in category and N = number of screened subjects

^b% = $100 \times n/N$, where n = number of treated subjects in category and N = number of subjects randomised

448, 674) and 602 mL (95% CI 489, 715) for AS MDI and Proventil, and an LS mean difference of -40 mL (90% CI $-77, -4$), which was contained within the predefined equivalence bounds of ± 200 mL (Table 3).

3.2.2 Extrapulmonary Pharmacodynamic Results

AS MDI was associated with numerically lower maximum LS mean changes from baseline and time-weighted average changes from baseline after the last cumulative dose than Proventil for the following extrapulmonary pharmacodynamic parameters: QTcF (maximum LS mean difference [LSMD]: -5.71 ms; 90% CI $-11.07, -0.35$; time-weighted LSMD: -1.13 ms; 90% CI $-3.55, 1.28$), heart rate (maximum LSMD: -3.81 beats per minute [bpm]; 90% CI $-6.26, -1.37$; time-weighted LSMD: -2.27 bpm; 90% CI $-3.73, -0.81$), and serum glucose (maximum LSMD: -1.56 mg/dL; 90% CI $-7.93, 4.81$; time-weighted LSMD: -1.73 mg/dL; 90% CI $-5.43, 1.97$) (Table 4). Maximum LS mean changes from baseline and time-weighted average changes from baseline were slightly higher with AS MDI versus Proventil for both SBP (maximum LSMD: 0.28 mm Hg; 90% CI $-1.86, 2.42$; time-weighted LSMD: 0.92 mm Hg; 90% CI $-0.69, 2.53$) and DBP (maximum LSMD:

Table 2 Baseline demographics for both the ASPEN and ANTORA studies

Parameter	ASPEN (<i>n</i> = 45)	ANTORA (<i>n</i> = 80)
Age, years, mean (SD)	34.2 (7.4)	42.6 (13.7)
Male sex, <i>n</i> (%)	23 (51.1)	37 (46.2)
Race, white, <i>n</i> (%)	34 (75.6)	59 (73.8)
BMI, kg/m ² , mean (SD)	28.6 (6.0)	28.0 (5.2)
Duration of asthma, years, mean (SD)	24.8 (9.6)	28.3 (14.5)
Prior asthma medication, <i>n</i> (%)		
As-needed SABA alone	19 (42.2)	44 (55.0)
ICS	3 (6.7)	7 (8.8)
ICS/LABA	23 (51.1)	29 (36.3)
FEV ₁ , L, mean (SD)		
Pre-bronchodilator	2.31 (0.60)	2.26 (0.58)
Post-bronchodilator	2.96 (0.72)	2.79 (0.71)
FEV ₁ , % predicted, mean (SD)		
Pre-bronchodilator	63.58 (8.66)	68.03 (10.94)
Post-bronchodilator	81.73 (10.20)	-
Reversibility, %, mean (SD)	29.3 (13.1)	25.8 (10.6)

BMI body mass index, FEV₁ forced expiratory volume in 1 second, ICS inhaled corticosteroid, LABA long-acting β₂-agonist, mITT modified intent-to-treat, SABA short-acting β₂-agonist, SD standard deviation

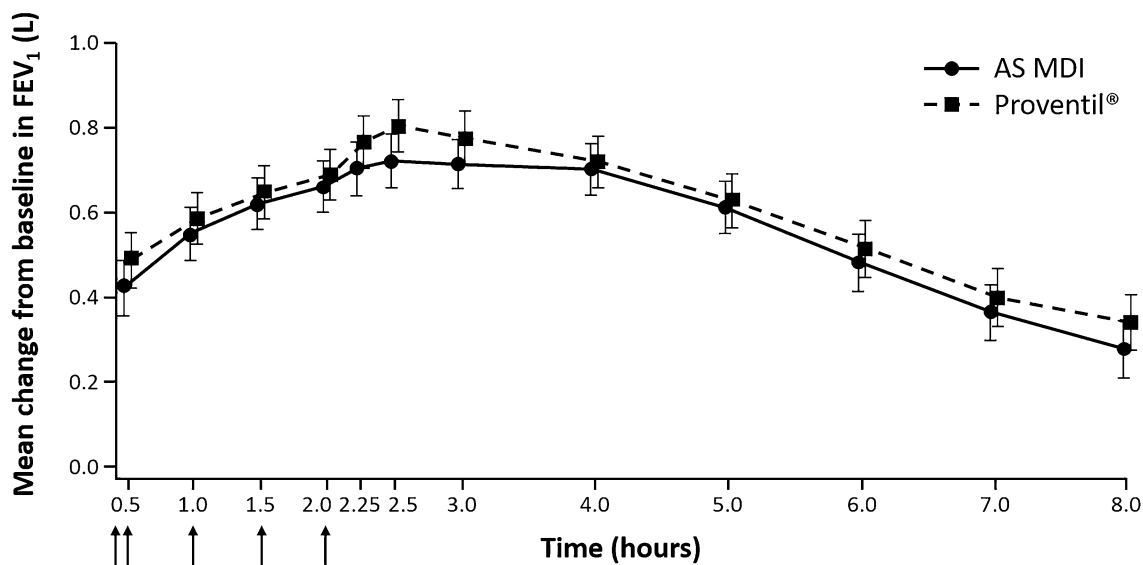


Fig. 1 Adjusted mean change from baseline in FEV₁ (\pm SE) (L) 30 minutes after each cumulative dose and 6 h after the final cumulative dose (mITT analysis population) in the ASPEN study. Arrows indi-

cate when each of the 5 doses was given. AS albuterol sulfate, FEV₁ forced expiratory volume in 1 second, MDI metered-dose inhaler, mITT modified intent-to-treat, SE standard error

0.47 mm Hg; 90% CI – 1.28, 2.22; time-weighted LSMD: 1.01 mm Hg; 90% CI – 0.15, 2.16) (Table 4). Maximum LS mean changes from baseline and time-weighted average changes from baseline after the last cumulative dose for serum potassium were similar between AS MDI and Proventil (maximum: LSMD: 0.07 mmol/L; 90% CI 0.00, 0.13; time-weighted: LSMD: – 0.01 mmol/L; 90% CI – 0.08, 0.07) (Table 4).

3.2.3 Pharmacokinetic Results

Mean $C_{15\text{min}}$ of plasma albuterol for both AS MDI and Proventil increased with increasing cumulative doses until the final dose (~2 h after the first cumulative dose) (Fig. 2). However, following the final cumulative dose, a sharp increase in plasma albuterol concentration was observed with Proventil, which was followed by a steep decline, while

Table 3 Change from baseline in FEV₁ (mL) 30 minutes after each cumulative dose (mITT analysis set) and FEV₁ AUC₀₋₆ (time averaged after the final dose) in the ASPEN study

Parameter	AS MDI (n=45) LS mean (95% CI)	Proventil® (n=45) LS mean (95% CI)	Difference vs Proventil LS mean (90% 95% CI) ^a
Change from baseline in FEV ₁ (mITT analysis set) cumulative dose			
90 µg	421 (300, 543)	488 (367, 610)	- 67 (- 130, - 4)
180 µg	548 (432, 665)	586 (469, 702)	- 38 (- 86, 10)
360 µg	619 (502, 737)	647 (529, 765)	- 28 (- 83, 28)
720 µg	659 (544, 775)	690 (575, 805)	- 31 (-80, 19)
1440 µg	721 (602, 840)	805 (686, 925)	- 84 (- 148, - 21)
Change from baseline in FEV ₁ AUC ₀₋₆ (time averaged)			
LS mean (SE)	561 (56.2)	602 (56.2)	- 40 (- 77, - 4)

AS albuterol sulfate, AUC₀₋₆ area under the curve from 0 to 6 h, CI confidence interval, FEV₁ forced expiratory volume in 1 second, LS least squares, MDI metered-dose inhaler, mITT modified intent-to-treat

^aEquivalence was assessed by comparing the 90% CIs to bounds of ± 200 mL

Table 4 Maximum change from baseline in extrapulmonary pharmacodynamic parameters over the 6 h following final cumulative dose (per protocol analysis set) and time-weighted average changes from baseline after the last cumulative dose in the ASPEN study

Parameter	AS MDI LS mean (95% CI)	Proventil® LS mean (95% CI)	Difference vs Proventil LS mean (90% CI)
Maximum change from baseline			
QTcF (ms)	17.732 (13.206, 22.259) n = 45	23.439 (18.964, 27.915) n = 46	- 5.707 (- 11.069, - 0.345)
Heart rate (bpm)	17.606 (14.200, 21.012) n = 45	21.418 (18.036, 24.801) n = 46	-3.812 (- 6.255, - 1.369)
Diastolic BP (mm Hg) ^a	- 10.722 (- 12.294, - 9.149) n = 45	- 11.191 (- 12.746, - 9.637) n = 46	0.470 (- 1.281, 2.220)
Systolic BP (mm Hg)	11.108 (8.656, 13.560) n = 45	10.828 (8.398, 13.258) n = 46	0.280 (- 1.856, 2.416)
Serum glucose (mg/dL)	44.733 (35.871, 53.596) n = 40	46.293 (37.565, 55.020) n = 42	- 1.559 (- 7.925, 4.807)
Serum potassium (mmol/L) ^a	- 0.733 (- 0.833, - 0.633) n = 39	- 0.798 (- 0.896, - 0.699) n = 41	0.065 (0.000, 0.129)
Time-weighted average changes from baseline			
QTcF (ms)	4.287 (1.643, 6.932) n = 45	5.421 (2.802, 8.041) n = 46	- 1.134 (- 3.545, 1.277)
Heart rate (bpm)	8.034 (5.475, 10.593) n = 45	10.301 (7.754, 12.848) n = 46	- 2.267 (- 3.727, - 0.807)
Diastolic BP (mm Hg) ^a	- 3.271 (- 4.633, - 1.908) n = 45	- 4.280 (- 5.631, - 2.929) n = 46	1.009 (- 0.146, 2.164)
Systolic BP (mm Hg)	1.365 (- 0.546, 3.276) n = 45	0.442 (- 1.452, 2.337) n = 46	0.922 (- 0.688, 2.533)
Serum glucose (mg/dL)	17.348 (12.332, 22.365) n = 40	19.077 (14.141, 24.014) n = 42	- 1.729 (- 5.429, 1.971)
Serum potassium (mmol/L) ^a	- 0.461 (- 0.556, - 0.366) n = 39	- 0.451 (- 0.545, - 0.358) n = 41	- 0.009 (- 0.084, 0.065)

AS albuterol sulfate, CI confidence interval, BP blood pressure, LS least squares, MDI metered-dose inhaler, SE standard error, QTcF Fredericia-corrected QT interval

^aData are lowest values of post-dose assessment minus baseline. Therefore, negative signs indicate the direction of change

in contrast, mean plasma albuterol concentration remained stable during the hour after the final cumulative dose of AS MDI, indicating a longer absorption time. At all time points, mean albuterol concentrations were lower with AS MDI versus Proventil (Fig. 2).

The systemic exposure of albuterol was numerically lower for AS MDI versus Proventil following inhalation of cumulative doses (Table 5). The mean C_{max} and AUC_{0-t} of albuterol (measured to 14 h after the first cumulative dose) were numerically lower for AS MDI than Proventil (Table 5). The median T_{max} was similar between treatments, at 2.6 h after the first cumulative dose for AS MDI and 2.4 h after the first cumulative dose for Proventil (Table 5).

The bioavailability of albuterol was ~21% to 27% lower with AS MDI than with Proventil. The geometric mean ratio of AS MDI to Proventil for C_{max} was 72.61% (90% CI 66.48%, 79.30%) and for AUC_{0-t} was 78.83% (90% CI 73.39%, 84.67%).

3.3 ANTORA

3.3.1 Efficacy Results

Both doses of AS MDI and Proventil were statistically superior to placebo for the primary efficacy endpoint (change from baseline in $FEV_1 AUC_{0-6}$) and secondary efficacy endpoints (change from baseline in $FEV_1 AUC_{0-4}$ and peak change from baseline in FEV_1) (all $p < 0.0001$; Table 6). The LS mean differences of AS MDI 90 μ g and 180 μ g versus placebo were 134 mL ($p < 0.0001$) and 196 mL ($p < 0.0001$) for change from baseline in $FEV_1 AUC_{0-6}$ and 183 mL ($p < 0.0001$) and 250 mL ($p < 0.0001$) for change

Table 5 Albuterol pharmacokinetic parameters by treatment (pharmacokinetic analysis set) in the ASPEN study

Parameter	AS MDI ($n = 25$)	Proventil® ($n = 25$)
C_{max} , ng/mL, mean (SD)	3.8 (1.0)	5.5 (2.0)
AUC_{0-t} , ng·h/mL, mean (SD)	22.2 (6.0)	28.2 (7.6)
T_{max} , h, median (range)	2.6 (2.23–5.02)	2.4 (2.20–5.05)

AS albuterol sulfate, AUC_{0-t} area under the concentration-time curve from 0 to the time of the last measurable plasma concentration, C_{max} maximum plasma concentration, MDI metered-dose inhaler, T_{max} time to maximum plasma concentration

from baseline in $FEV_1 AUC_{0-4}$, respectively (Table 6). For Proventil 90 μ g and 180 μ g, LS mean differences versus placebo were 171 mL ($p < 0.0001$) and 212 mL ($p < 0.0001$) ($FEV_1 AUC_{0-6}$) and 217 mL ($p < 0.0001$) and 269 mL ($p < 0.0001$) ($FEV_1 AUC_{0-4}$), respectively (Table 6). For both endpoints, AS MDI was non-inferior to Proventil at both the 90 μ g and 180 μ g dose levels, as demonstrated by the 95% CIs for the difference (AS MDI vs Proventil) in $FEV_1 AUC_{0-6}$ and AUC_{0-4} being above the predefined non-inferiority margin of 100 mL (Table 6). For peak change from baseline in FEV_1 , AS MDI 90 μ g and 180 μ g doses were both statistically superior to placebo, with LS mean differences of 199 mL and 275 mL (both $p < 0.0001$) for the respective doses (Table 7). Similarly, Proventil 90 μ g and 180 μ g doses were also superior to placebo for this endpoint, with LS mean differences of 239 mL and 282 mL (both $p < 0.0001$), respectively (Table 7). Changes from baseline in FEV_1 over the 6 h post-administration of treatment were greater with 180 μ g versus 90 μ g for both AS MDI and Proventil (Fig. 3).

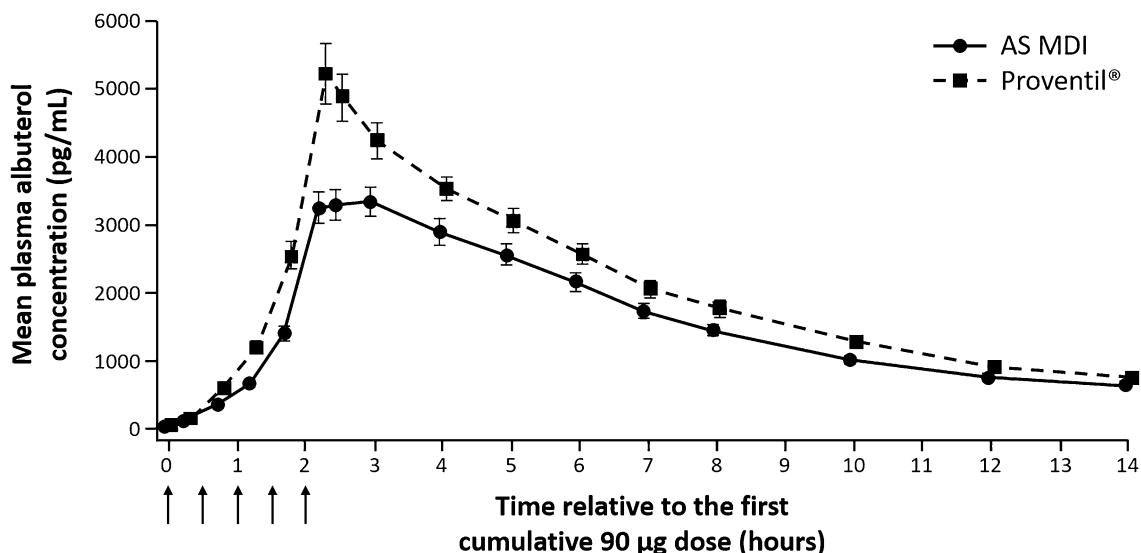


Fig. 2 Mean (\pm SE) plasma albuterol concentration-time profile (pharmacokinetic analysis set) in the ASPEN study. Arrows indicate when each of the 5 doses was given. AS albuterol sulfate, MDI metered-dose inhaler, MITT modified intent-to-treat, SE standard error

Table 6 Change from baseline in FEV₁ AUC₀₋₆ (mL) and FEV₁ AUC₀₋₄ (mITT analysis set) in the ANTORA study

Parameter	Placebo (<i>n</i> = 78)	AS MDI		Proventil®	
		90 µg (<i>n</i> = 79)	180 µg (<i>n</i> = 79)	90 µg (<i>n</i> = 78)	180 µg (<i>n</i> = 77)
Change from baseline in FEV ₁ AUC ₀₋₆ (mL)					
LS mean (SE)	70 (23.9)	203 (23.8)	266 (23.9)	240 (23.9)	282 (24.0)
Difference versus placebo					
LS mean (95% CI)	–	134 (93, 175)	196 (155, 237)	171 (130, 212)	212 (171, 253)
<i>p</i> value ^a	–	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Non-inferiority versus Proventil ^b					
LS mean (95% CI)	–	– 37 (– 78, 4)	– 16 (– 57, 25)	–	–
Change from baseline in FEV ₁ AUC ₀₋₄ (mL)					
LS mean (SE)	80 (25.4)	263 (25.3)	331 (25.4)	297 (25.4)	349 (25.5)
Difference versus placebo					
LS mean (95% CI)	–	183 (140, 226)	250 (207, 293)	217 (174, 260)	269 (225, 312)
<i>p</i> value ^a	–	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Non-inferiority versus Proventil ^b					
LS mean (95% CI)	–	– 34 (– 77, 9)	– 19 (– 62, 25)	–	–

AS albuterol sulfate, AUC₀₋₄ area under the curve from 0 to 4 h, AUC₀₋₆ area under the curve from 0 to 6 h, CI confidence interval, FEV₁ forced expiratory volume in 1 second, LS least squares, MDI metered-dose inhaler, mITT modified intent-to-treat, SE standard error

^a*p* values are for tests of superiority

^bComparisons were made against the equivalent dose of Proventil. Non-inferiority was concluded when the lower CI limit for the difference between treatments was greater than the predefined non-inferiority limit of 100 mL

Median times to onset of response (12% improvement in FEV₁) were comparable across the dose levels and formulations, at approximately 7 minutes for all active treatments. The percentages of subjects achieving a 12% improvement in FEV₁ were greater with all active treatment arms versus

placebo. This percentage was slightly higher with the 180 µg doses compared with the 90 µg doses for both AS MDI and Proventil (Table 7). Of the patients treated with AS MDI and Proventil, 61%–75% achieved ≥ 12% improvement, versus only 12.8% of patients receiving placebo.

Table 7 Peak change from baseline in FEV₁ (mL) and time to onset of 12% improvement in FEV₁ (mITT analysis set) in the ANTORA study

Parameter	Placebo (<i>n</i> = 78)	AS MDI		Proventil®	
		90 µg (<i>n</i> = 79)	180 µg (<i>n</i> = 79)	90 µg (<i>n</i> = 78)	180 µg (<i>n</i> = 77)
Peak change from baseline in FEV ₁ (mL)					
LS mean (SE)	233 (29.2)	433 (29.1)	509 (29.2)	472 (29.2)	516 (29.3)
Difference versus placebo					
LS mean (95% CI)	–	199 (155, 244)	275 (231, 320)	239 (194, 283)	282 (237, 327)
<i>p</i> value ^a	–	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Non-inferiority versus Proventil ^b					
LS mean (95% CI)	–	– 39 (– 84, 5)	– 7 (– 51, 38)	–	–
Time to onset of 12% improvement in FEV ₁ (minutes)					
<i>n</i> (%) with 12% improvement	10 (12.8)	53 (67.1)	57 (72.2)	48 (61.5)	58 (75.3)
Median (min, max)	15 (6.0, 36.0)	7.0 (4.0, 32.0)	7.0 (5.0, 31.0)	7.0 (4.0, 31.0)	7.0 (5.0, 34.0)

AS albuterol sulfate, CI confidence interval, FEV₁ forced expiratory volume in 1 second, LS least squares, MDI metered-dose inhaler, mITT modified intent-to-treat, SE standard error

^a*p* values are for tests of superiority

^bComparisons were made against the equivalent dose of Proventil. Non-inferiority was concluded when the lower CI limit for the difference between treatments was greater than the predefined non-inferiority limit of 100 mL

3.4 Safety and Tolerability

3.4.1 ASPEN

No deaths, serious treatment-emergent adverse events (TEAEs) or serious treatment-related AEs were reported during the study. Overall, the incidence of TEAEs was low and similar following cumulative doses of AS MDI (8/45; 17.8%) and Proventil (10/46; 21.7%) (Table 8). The majority of TEAEs were mild in severity. The most frequently reported treatment-related AEs included ‘feeling jittery’ and tremor and were reported during both AS MDI and Proventil treatment periods, with a greater proportion of patients reporting feeling jittery with Proventil (13.0% vs 6.7%) (Table 8). The overall incidence of TEAEs deemed to be treatment-related was 13.3% for AS MDI and 19.6% for Proventil (Table 8).

3.4.2 ANTORA

AS MDI and Proventil were well tolerated; safety findings were consistent with the known safety profile for albuterol [6, 9, 10]. Overall, the incidence of TEAEs was low across treatment groups, with no dose-related trends (Table 8). Only four TEAEs were reported in three patients all taking Proventil (Table 8). All TEAEs were mild in severity and none were considered treatment-related. No deaths, serious TEAEs or serious treatment-related AEs were reported.

4 Discussion

The results from ASPEN and ANTORA demonstrate that AS MDI is comparable to Proventil in improving lung function, and ANTORA also showed that both treatments are superior to placebo.

ASPEN demonstrated AS MDI was equivalent to Proventil for lung function improvement following cumulative doses of albuterol up to 1440 µg in patients with asthma, as measured by the primary and secondary efficacy endpoints. The bioavailability of albuterol was ~21%–27% lower with AS MDI versus Proventil. Extrapulmonary pharmacodynamic effects of albuterol were smaller in magnitude with AS MDI versus Proventil for changes from baseline in QTcF, heart rate and serum glucose, but were slightly higher with AS MDI for changes from baseline in SBP and DBP.

ANTORA demonstrated that the 90 µg and 180 µg doses of AS MDI and Proventil were significantly superior to placebo MDI for all primary and secondary efficacy endpoints. AS MDI was non-inferior to Proventil at both the 90 µg and 180 µg dose levels for primary and all secondary efficacy endpoints, with the 95% CIs for the observed differences between treatments all within the pre-specified non-inferiority limit of 100 mL. With both treatments, the magnitude of change from baseline for FEV₁ AUC₀₋₄ was greater than for the primary endpoint of FEV₁ AUC₀₋₆; however, this was expected, as albuterol is more pharmacodynamically active during the first 4 h after inhalation. Similar findings to the primary and secondary efficacy endpoints were observed with the other efficacy endpoints included in this study. In both ASPEN and ANTORA, all study treatments were well

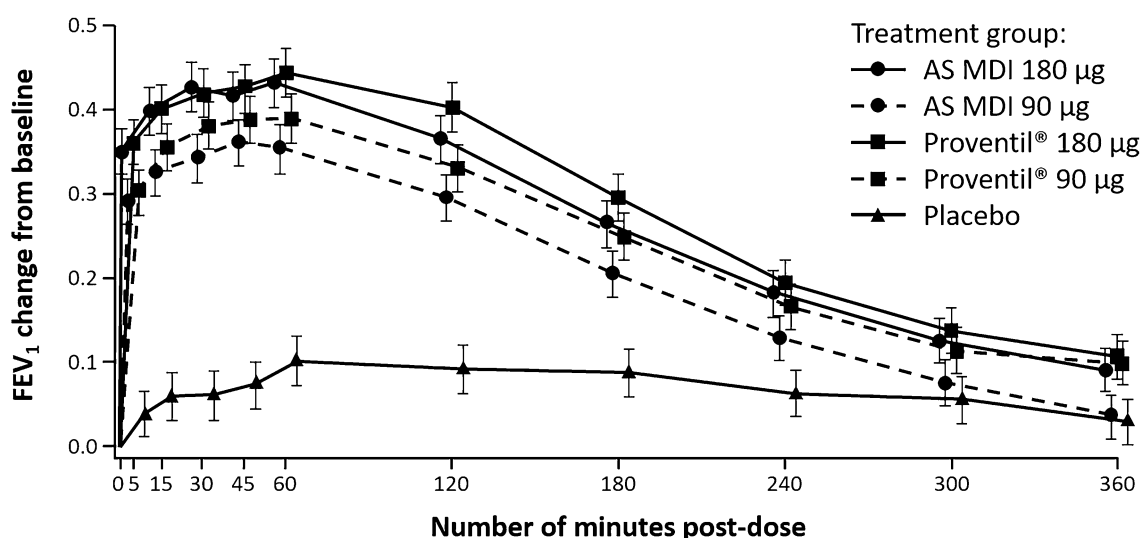


Fig. 3 Mean change from baseline in FEV₁ (L) over time (mITT analysis set) in the ANTORA study. Error bars represent SE. AS albuterol sulfate, FEV₁ forced expiratory volume in 1 second, MDI metered-dose inhaler, mITT modified intent-to-treat, SE standard error

Table 8 Overall summary of TEAEs in ASPEN and ANTORA

Parameter	ASPEN		ANTORA				
	AS MDI (N = 45)	Proventil® (N = 46)	Placebo MDI (N = 82)	AS MDI 90 µg (N = 81)	AS MDI 180 µg (N = 81)	Proventil 90 µg (N = 82)	Proventil 180 µg (N = 79)
≥ 1 TEAE, n (%)	8 (17.8)	10 (21.7)	0	0	0	1 (1.2)	2 (2.5)
Treatment-related TEAEs, n (%)	6 (13.3)	9 (19.6)	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0	0
Deaths (all causes), n (%)	0	0	0	0	0	0	0
TEAEs occurring in ≥ 2% of patients							
Feeling jittery	3 (6.7)	6 (13.0)	0	0	0	0	0
Tremor	2 (4.4)	2 (4.3)	0	0	0	0	0
Headache	2 (4.4)	0	0	0	0	0	0
Blood potassium decreased	0	1 (2.2)	0	0	0	0	0
Dizziness	1 (2.2)	0	0	0	0	0	0
Epistaxis	0	1 (2.2)	0	0	0	0	0
Vomiting	1 (2.2)	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	1 (1.3)
Chills	0	0	0	0	0	0	1 (1.3)
Nausea	0	0	0	0	0	0	1 (1.3)
Tuberculin test positive	0	0	0	0	0	1 (1.2)	0

AS albuterol sulfate, MDI metered-dose inhaler, TEAE treatment-emergent adverse event

tolerated, and safety findings were consistent with the known safety profile of albuterol [6, 9, 10].

In ASPEN, treatment with Proventil demonstrated greater effects on systemic exposure, extrapulmonary pharmacodynamic and safety parameters versus AS MDI; a possible explanation could be that Proventil contains oleic acid and ethanol. Oleic acid has been shown to increase pulmonary absorption of protein, while the inclusion of ethanol may dissolve some of the albuterol in suspension, thus resulting in more rapid absorption [11, 12]. These additives may explain the increased systemic exposure, thus increasing extrapulmonary effects of Proventil versus AS MDI. This could also explain the sharp peak in albuterol plasma concentrations following the final cumulative dose from Proventil, while AS MDI had a more prolonged absorption period. Proventil is currently the only formulation of albuterol to contain these additional compounds/absorption enhancers [13].

The ASPEN results were compared to a study with a similar trial design investigating two albuterol products, ProAir RespiClick® and ProAir® HFA [7]. Evaluation of lung function, measured after each cumulative dose, found that AS MDI was comparable to both ProAir products. At a cumulative dose of 90 µg, LS mean (standard error) FEV₁ was 421 (60) mL for AS MDI, 420 (76) mL for ProAir RespiClick® and 480 (76) mL for ProAir® HFA, and at a cumulative dose of 1440 µg, FEV₁ was 721 (59) mL, 690 (76) mL and 720 (76) mL, respectively. AS MDI was similarly comparable to

both ProAir products following evaluation of the pharmacokinetic results; the geometric LS mean AUC_{0-t} was 21.5 ng·h/mL with AS MDI, 23.2 ng·h/mL for ProAir RespiClick® and 20.9 ng·h/mL for ProAir® HFA. The geometric LS mean C_{max} was 3.71 ng/mL, 4.42 ng/mL and 3.30 ng/mL for AS MDI, ProAir RespiClick® and ProAir® HFA, respectively.

AS MDI 180 µg was well tolerated and produced similar bronchodilator effects to Proventil 180 µg in adult and adolescent patients with asthma. The data presented on the efficacy and safety of AS MDI support the selection of AS MDI 180 µg for a Phase III drug trial.

5 Conclusions

The bronchodilator effects of albuterol delivered via AS MDI using novel Co-Suspension Delivery™ Technology and Proventil were equivalent, both following dose-ranging and cumulative doses of albuterol up to 1440 µg. AS MDI was well tolerated, with numerically smaller extrapulmonary effects and lower systemic exposure versus Proventil. The findings from these Phase II efficacy and safety studies support selection of AS MDI 180 µg to be taken into Phase III clinical trials, either alone or in combination with ICS (SABA/ICS; PT027) and may facilitate development of novel inhalers combining rescue and controller therapies to benefit patients with asthma.

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Declarations

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Role of the Funding Source AstraZeneca funded the study and had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Conflict of Interest AM, CC, CR, KR and MG are employees of, and own stock in, AstraZeneca. CLF has received payments from 4D Pharma PLC, Amphastar, Boehringer Ingelheim, Bond Avillion 2 Development LP, Bosch Healthcare Solutions GmbH, Cipla Ltd, GlaxoSmithKline, Knopp Biosciences LLC, Novartis Research and Development, Romark, Sanofi US Services Inc, Teva Pharmaceuticals Ltd and Vorso Corp. EK has performed consulting, served on advisory boards, and received travel reimbursement from Amphastar, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Novartis, Sunovion and Theravance. He has conducted multicentre clinical research trials for some 40 pharmaceutical companies.

Data Availability Statement Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharm.acm.com/ST/Submission/Disclosure>.

Ethics Approval This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements.

Consent to Participate The Investigator was responsible for obtaining written informed consent (and assent, where applicable) from potential subjects before any study-specific screening and entry into the study. After the subject signed the ICF (and/or assent form, where applicable), the original was retained by the Investigator; the subject retained a copy.

Consent for Publication Not applicable.

Author Contributions CC: Conceptualisation; data curation; investigation; methodology; supervision; validation; visualisation; roles/writing—original draft; writing—review and editing. AM: Conceptualisation; investigation; methodology; supervision; validation; visualisation; roles/writing—original draft; writing—review and editing. KR: Conceptualisation; investigation; methodology; project administration; resources; supervision; validation; roles/writing—original draft; writing—review and editing. MG: Conceptualisation; investigation; methodology; supervision; validation; visualisation; writing—review and editing. CLF: Data curation; methodology; writing—review and editing.

ing. EK: Data curation; investigation; methodology; writing—review and editing. CR: Conceptualisation; funding acquisition; methodology; supervision; validation; writing—review and editing.

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