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Albuterol/budesonide for the treatment of exercise-induced bronchoconstriction in patients with asthma

The TYREE study

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ABSTRACT

Background: PT027 is a fixed-dose combination of albuterol (salbutamol) and budesonide in a single pressurized metered-dose inhaler.
Objective: To evaluate the efficacy and safety of albuterol/budesonide compared with placebo in patients with asthma and exercise-induced bronchoconstriction (EIB).
Methods: In this randomized, double-blind, 2-period, single-dose crossover study, adolescents and adults with asthma and EIB (defined by ≥20% decrease from pre-exercise challenge forced expiratory volume in 1 second [FEV_1]) were randomized to albuterol/budesonide (180/160 μg) followed by placebo (n = 29) or the reverse sequence (n = 31). Subjects were stratified by background therapy (as-needed short-acting β_2-agonist alone or low-to-medium dose inhaled corticosteroid plus as-needed short-acting β_2-agonist). FEV_1 was measured 5 minutes pre-dose, 30 minutes postdose (5 minutes pre-exercise challenge [baseline]), and 5, 10, 15, 30, and 60 minutes postexercise. The primary end point was maximum percentage fall from baseline in FEV_1 up to 60 minutes postexercise challenge.
Results: Least squares mean maximum percentage fall in FEV_1 up to 60 minutes postexercise challenge was 5.45% with albuterol/budesonide vs 18.97% with placebo (difference, −13.51% [95% confidence interval, −16.94% to −10.09%]; $P < .001$). More subjects were fully protected (maximum percentage fall in FEV_1 post-exercise challenge < 10%) with albuterol/budesonide than with placebo (78.3% vs 28.3%; $P < .001$). The treatment effect was consistent irrespective of background inhaled corticosteroid therapy, and albuterol/budesonide was well tolerated.
Conclusion: In adolescents and adults with asthma and EIB, a single dose of albuterol/budesonide 180/160 μg taken approximately 30 minutes before exercise was significantly more effective than placebo in preventing EIB.
Trial Registration: ClinicalTrials.gov Identifier: NCT04234464

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Introduction

Exercise-induced bronchoconstriction (EIB) is an acute narrowing of the airways, with both an airway smooth muscle (ASM) and an inflammatory component, that occurs as a result of exercise and affects a substantial proportion of patients with asthma.[1] The exact prevalence of EIB in patients with asthma is not known,[1] as there is no reference standard for diagnosis,[2] although it is most often identified by a drop in forced expiratory volume in 1 second (FEV_1) of greater than or equal to 20% after exercise.[2] This fall in lung function normally begins within 2 to 5 minutes post-exercise, reaches a peak after 10 minutes, and resolves within approximately 60 minutes.[3]

Recommendations for controlling EIB include administering an inhaled short-acting β_2-agonist (SABA) at least 15 minutes before exercise[1] to provide rapid relief of asthma symptoms and reduce or prevent EIB.[1,4] For patients who continue to have symptoms in response to exercise despite use of preventive pre-exercise SABA, or who need a SABA daily or more frequently, daily maintenance treatment with an inhaled corticosteroid (ICS) or a leukotriene receptor antagonist is strongly recommended.[1]

PT027 is a fixed-dose combination of the SABA, albuterol, and the ICS, budesonide, in a single pressurized metered-dose inhaler (pMDI). Developed as a novel rescue therapy for the treatment of asthma, it combines the rapid bronchodilation provided by SABA with the anti-inflammatory properties of ICS. The use of SABA alone as rescue may leave patients at risk of severe exacerbations,[5,6] but by addressing airway inflammation, ICS-containing medications may help reduce the risk.[7] A single dose of ICS has been found to potentiate the effects of SABA on ASM relaxation in patients with mild asthma,[8] which has mechanistic implications for EIB, in which ASM contraction is a key pathophysiological element.[3] In addition, a single dose of ICS has been found to acutely improve lung function (FEV_1) response to SABA when administered concurrently in patients with asthma[9] and to reverse β_2-adrenergic receptor tolerance and desensitization in vitro.[10]

Phase 2 studies of albuterol pressurized inhalation suspension delivered by MDI revealed an equivalent effect on bronchodilation to Proventil with no new safety findings identified.[11] These data supported the selection of albuterol MDI 180 μg for phase 3 studies in combination with an ICS. PT027 is currently in clinical development as an albuterol/ICS rescue medication for asthma, with the aim of providing acute relief from bronchospasm and reducing the risk of severe exacerbations. Patients with EIB and asthma, who experience symptoms with exercise and use their SABA reliever therapy prophylactically before exercise to prevent EIB, may benefit from using the same fixed-dosed combination of albuterol/ICS rescue treatment, taken before exercise.

In this first published phase 3 study of albuterol/budesonide, we evaluated the efficacy and safety of single-dose albuterol/budesonide pMDI (albuterol 180 μg/budesonide 160 μg) compared with placebo pMDI in adolescents and adults with asthma and EIB with or without ICS maintenance therapy.

Methods

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, 2-period, single-dose, crossover study (NCT04234464). Subjects were randomized 1:1 to the following 1 of 2 treatment sequences: A/B or B/A, where A is albuterol/budesonide pMDI 180/160 μg (given as 2 inhalations of 90/80 μg) (AstraZeneca, Sweden) and B is placebo pMDI (2 inhalations) (AstraZeneca, Sweden). Both pMDIs used the Aerosphere Co-suspension Delivery Technology, ensuring consistent dose delivery.[12]

The study consisted of 2 screening visits (SV1 and SV2), 2 treatment visits (TV1 and TV2), and a final follow-up visit that was conducted by a telephone call 3 to 5 days after the final study visit (Fig 1). At each visit, standardized exercise challenge tests (ECTs) on a treadmill were conducted and standard FEV_1 spirometry assessments were performed relative to ECT and dosing (before and after), as applicable.[13,14] Subjects were required to demonstrate EIB at SV1 through standardized ECT, which was confirmed at SV2 with administration of placebo pMDI 30 minutes before the ECT.

Randomization was centralized and stratified by age (adolescents aged 12–17 and adults aged 18–70 years) and background ICS therapy (as-needed SABA alone or ICS plus as-needed SABA). A randomization schedule was generated by a designated statistician, and, on enrollment, subjects were assigned a unique identification code, automatically generated by the electronic data capture system (Rave Web Based Data Capture) based on the order of entry. Subject information was then integrated into the Interactive Web Response System (Randomization and Trial Supply Management) for randomization.

Blinding was maintained until all subjects had completed the treatment phase and the database locked. The randomization code was not available to the study team, study center personnel, sponsor monitors, sponsor project statisticians, or any other personnel employed or affiliated with the sponsor, and investigators and subjects until after the database had been locked. The 2 different kit types of investigational product and placebo were visually identical to protect the blinding.

The study was conducted in accordance with the International Conference on Harmonization guidelines.

Subjects

Adolescents and adults were included if they had a documented history of asthma (as defined by the Global Initiative for Asthma criteria) for more than or equal to 6 months before SV1 and EIB. Subjects were required to be receiving as-needed SABA or stable dosing of low-to-medium dose maintenance therapy with ICS plus as-needed SABA for at least 4 weeks before SV1. No other asthma therapies were permitted during the study.

Subjects were required to demonstrate EIB, as defined by a greater than or equal to 20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge at SV1 and SV2. To be eligible for the treatment phase of the study, subjects were also required at SV1 to demonstrate a pre-exercise challenge best FEV_1 greater than or equal to 70% of predicted value and EIB, as found by a greater than or equal to 20% decrease from the 5-minute pre-exercise challenge absolute FEV_1. At SV2, subjects were required to meet the same criteria as at SV1, including having a pre-placebo dose, pre-exercise challenge best FEV_1 value measured not exceeding plus or minus 20% of the pre-exercise challenge best FEV_1 value measured at SV1, and a post-placebo dose, pre-exercise challenge best FEV_1 greater than or equal to 70% of predicted value. No development of a respiratory tract infection or asthma exacerbation between SV1 and SV2 was permitted. If any of the spirometry criteria were not met at SV1 or SV2, subjects could be retested within 2 to 10 days of the initial visit.

At TV1 and TV2, subjects were also required to continue to meet the following criteria: (1) pre-dose, pre-exercise challenge best FEV_1 greater than or equal to 70% of predicted value; (2) pre-dose, pre-exercise challenge best FEV_1 value measured not exceeding plus or minus 20% of the pre-exercise challenge best FEV_1 value measured at SV1; and (3) post-dose, pre-exercise challenge best FEV_1 greater than or equal to 70% of predicted value.

Exclusion criteria for the study included chronic obstructive pulmonary disease or other significant lung disease, including any disease requiring regular or occasional use of oxygen. Subjects were also excluded if they had any systemic corticosteroid use within 3 months

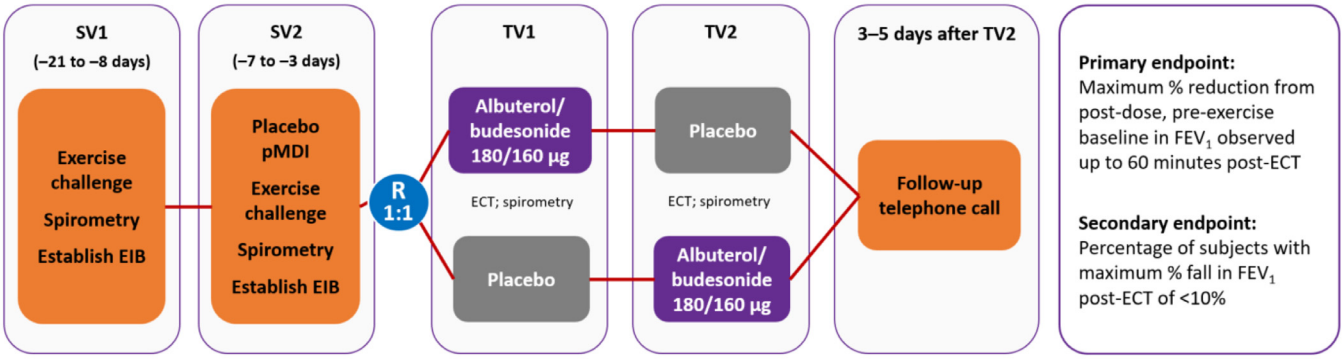

Figure 1. Study design. Enrolled 60 subjects, 31 receiving only as-needed SABA (non-ICS group) and 29 receiving low-to-medium doses of ICS plus as-needed SABA (ICS group).3-7-day washout between Visit 3 and 4. ECT, exercise challenge test; EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; pMDI, pressurized metered-dose inhaler; R, randomization; SABA, short-acting β_2-agonists; SV, screening visit; TV, treatment visit.

of SV1, any regular asthma maintenance treatment with therapies other than the permitted SABA and ICS treatment within 1 month of SV1, or if they were current or former smokers with more than 10 pack-year history or former smokers who stopped smoking within 6 months of SV1.

Spirometry and Exercise Challenge Test

At SV1, spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines[14] to determine baseline FEV_1. Pre- and post-exercise FEV_1 were measured at SV1 at 35- and 5-minutes pre-exercise and 5, 10, 15, 30, and 60 minutes post-exercise. Pre-dose, post-dose, and post-exercise FEV_1 were measured at SV2 and both treatment visits at 5 minutes pre-dose, 30 minutes post-dose (at the time of ECT), and 5, 10, 15, 30, and 60 minutes post-exercise. Spirometry assessments were performed using MasterScope equipment provided by eResearch Technology (Philadelphia, Pennsylvania). A centralized spirometry data collection system incorporating a quality control program was used to reduce FEV_1 variability between and within subjects and between study sites.

All spirometry measurements were made with the subject in the same position, and subjects rested for more than or equal to 15 minutes before the initial test. For each pre-dose and pre-exercise challenge spirometry, a maximum of 8 maneuvers were performed, with the highest value obtained from 3 acceptable and 2 repeatable spirometry maneuvers used. For the pre-dose assessments, FEV_1 and forced vital capacity, repeatability was required. For each post-exercise challenge spirometry, the highest value of 2 acceptable spirograms was used.

At SV1, subjects also performed a standardized ECT on a treadmill according to the American Thoracic Society/European Respiratory Society guidelines.[13] This was of 6 to 8 minutes of duration at approximately 80% to 95% of maximal heart rate (ie, 220 beats per minute minus age in years). Subjects conducted the test with a face mask which provided ambient dry air (20°C to 25°C). The ECT was performed at approximately the same time at each visit, and subjects rested for more than or equal to 15 minutes before. Heart rate was monitored continuously during the ECT until 60 minutes after completion.

Subjects were not allowed to perform physical exercise during the previous 24 hours, had to avoid large meals more than or equal to 2 hours before a study visit, and were not to consume caffeine-containing foods and beverages for more than or equal to 6 hours before and for the duration of each study visit. At SV2 and TV1 and TV2, subjects were administered the investigational product (placebo pMDI at SV2) and performed a standardized ECT on a treadmill, as described previously, 30 minutes after. Subjects were restricted from SABA within 6 hours before any lung function testing or exercise testing. There were no such restrictions on the use of ICS.

Objectives and End Points

The main study objective was to evaluate the efficacy of a single dosage of albuterol/budesonide (180/160 µg) compared with placebo on the protection from EIB in adolescent and adult patients with asthma. The primary end point was the mean maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge. Post-dose, pre-exercise baseline FEV_1 was defined as the 30 minutes post-dose value, that is, 5 minutes before exercise challenge, at each visit for the respective treatment.

The secondary end point was the proportion of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of less than 10% up to 60 minutes, representing the proportion of subjects fully protected from EIB.

Exploratory end points included the percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of less than 20% up to 60 minutes. This comprised the proportion of both fully (<10%) and partially (≥10% to <20%) protected subjects. Another exploratory end point was median time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post-dose, pre-exercise challenge baseline FEV_1. The percentage fall from baseline in FEV_1 at each time point within 60 minutes post-exercise challenge was also evaluated, as was the change from post-dose, pre-exercise baseline FEV_1 area under the curve from 0 to 30 minutes ($AUC_{0\text{-}30\ min}$) post-exercise challenge.

Safety end points included frequency and type of adverse events (AEs) and serious adverse events.

Subjects were stratified based on ICS background therapy, and the study was type I error controlled for the overall population and subjects taking as-needed SABA alone or ICS maintenance therapy plus as-needed SABA.

Statistical Analyses

Power calculations were based on the properties of the primary end point. A sample size of 30 subjects in each subgroup was chosen to provide a 92% probability to detect a difference of −9% between albuterol/budesonide and placebo, within each of the 2 subgroups of interest (background as-needed SABA alone and low-to-medium dose ICS maintenance therapy), assuming 2-sided, 5% level tests and a within-subject SD of 10%. Randomization of 60 subjects in total was

chosen to provide more than 99% overall probability to detect this difference. Because all subjects randomized in the study were receiving background therapy for asthma, a more conservative estimate of variability and treatment effect was assumed compared with studies of similar design.[15]

The primary end point of maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge was analyzed with a mixed effects model. This included categorical fixed effects for treatment, treatment period, treatment sequence, period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1, and a random subject within treatment sequence effect.

A hierarchical testing strategy was implemented to control the overall type I error rate at 5%.[16,17] This included for the overall population and for the subgroup analyses of subjects taking background as-needed SABA alone (non-ICS) and those receiving low-to-medium dose ICS maintenance therapy. Treatment comparisons were performed in the following sequence: overall population, non-ICS subgroup, and ICS subgroup. If a comparison was significant (alpha = 0.05, 2-sided), testing proceeded to the next comparison, stopping if a nonstatistically significant result occurred. The secondary and exploratory end points were not controlled for multiplicity; hence, they are presented for descriptive purposes only.

The secondary end point of maximum percentage fall in FEV_1 post-exercise challenge of less than 10% was analyzed using a generalized linear mixed model with logit link function to compare the treatments. The model was adjusted with fixed effects for treatment, treatment period and treatment sequence, period-specific pre-dose baseline FEV_1, average pre-dose baseline FEV_1, and a random subject within treatment sequence effect.

The exploratory end point of maximum percentage fall in FEV_1 post-exercise challenge of less than 20% was analyzed using a similar approach.

The exploratory end point, median time to recovery, was reported descriptively by treatment. *P* values were calculated using Prescott's period-adjusted sign test.[18] All FEV_1 efforts produced by a subject were considered to estimate the end point. Subjects who did not have at least 1 fall greater than 10% of the post-dose, pre-ECT baseline during the 60-minute period was considered protected and therefore left-censored at 0 minutes. Subjects who did not recover by 60 minutes were right-censored. Recovery was defined as FEV_1 measurements returning to within 10% of the post-dose, pre-exercise baseline result.

The exploratory end point, post-exercise FEV_1 $AUC_{0\text{-}30\ min}$, was analyzed with a mixed effects model similar to that used for the primary end point.

Results

Subject Demographics

A total of 131 subjects were screened, with 60 randomized; 29 to albuterol/budesonide/placebo and 31 to placebo/albuterol/budesonide (Fig 2). Of those randomized, 29 (48.3%) were receiving ICS background therapy; 70.0% were receiving low-dose ICS and 30.0% were receiving medium-dose ICS.[4] The mean age (± SD) of subjects was 40.5 (± 11.76) years, including 2 adolescent subjects aged 12 to 17 years, and 63.3% were of female sex. Detailed demographic characteristics are in Table 1.

Maximum Percentage Fall From Post-Dose, Pre-Exercise Challenge Test Baseline in Forced Expiratory Volume in 1 second

Use of albuterol/budesonide resulted in a significantly lower least square (LS) mean maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge (5.45%) than with placebo (18.97%). The difference in LS means was −13.51% (95% confidence interval [CI], −16.94% to −10.09%; $P < .001$) (Fig 3). In the non-ICS group, LS mean maximum percentage fall was 4.27% with albuterol/budesonide and 19.99% with placebo (difference, −15.73%; 95% CI, −20.61% to −10.84%; $P < .001$) (Fig 3). In the ICS group, LS mean maximum percentage fall was 6.65% with albuterol/budesonide and 18.00% with placebo (difference, −11.35%; 95% CI, −16.18% to −6.52%; $P < .001$) (Fig 3). The mean percentage fall from post-dose, pre-exercise baseline in FEV_1 by time point for each group is found in Figure 4.

Maximum Percentage Fall From Post-Dose, Pre-Exercise Challenge Test Baseline Forced Expiratory Volume in 1 second (<10% Fall in Forced Expiratory Volume in 1 second Responder Analysis; Fully Protected Subjects)

Overall, more subjects (78.3%, n = 47) were fully protected with albuterol/budesonide than with placebo (28.3%, n = 17). The odds ratio (OR) for full protection from EIB with albuterol/budesonide vs placebo was 10.55 (95% CI, 4.31-25.81; $P < .001$) (Fig 5). In the non-ICS group, 80.6% (n = 25) of the subjects were fully protected with albuterol/budesonide compared with 25.8% (n = 8) with placebo (OR, 14.58; 95% CI, 3.84-55.38; $P < .001$). In the ICS group, 75.9% (n = 22) of the subjects were fully protected with albuterol/budesonide vs 31.0% (n = 9) with placebo (OR, 8.11; 95% CI, 2.34-28.12; $P = .001$) (Fig 5).

Maximum Percentage Fall From Post-Dose, Pre-Exercise Challenge Test Baseline Forced Expiratory Volume in 1 second (<20% Fall in Forced Expiratory Volume in 1 second Responder Analysis; at Least Partially Protected Subjects)

Overall, more subjects (90.0%, n = 54) were at least partially protected with albuterol/budesonide than with placebo (51.7%, n = 31) (OR, 10.85; 95% CI, 3.70-31.80; $P < .001$) (Fig 5). In the non-ICS group, 90.3% (n = 28) of the subjects were at least partially protected with albuterol/budesonide vs 48.4% (n = 15) with placebo (OR, 14.78; 95% CI, 3.09-70.76; $P = .001$). In the ICS group, 89.7% (n = 26) of the subjects were at least partially protected with albuterol/budesonide compared with 55.2% (n = 16) with placebo (OR, 8.41; 95% CI, 1.84-38.59; $P = .007$) (Fig 5).

Time to Recovery in Post-Exercise Forced Expiratory Volume in 1 second

In total, 39 (65.0%) subjects had shorter times to recovery (a first measured FEV_1 value within 10% of baseline) associated with albuterol/budesonide compared with 11 (18.3%) associated with placebo ($P < .001$); median time to recovery post-ECT was 25.0 minutes faster for subjects treated with albuterol/budesonide than with placebo. In the non-ICS group, 21 (67.7%) subjects receiving albuterol/budesonide had shorter times to recovery compared with 6 (19.4%) subjects receiving placebo ($P = .011$); median time to recovery post-ECT was 30.0 minutes faster with albuterol/budesonide. In the ICS group, there were 18 (62.1%) subjects who had shorter times to recovery associated with albuterol/budesonide and 5 (17.2%) with shorter recovery times associated with placebo ($P = .02$); median time to recovery post-ECT was 12.0 minutes faster with albuterol/budesonide.

Change From Post-Dose, Pre-Exercise Baseline Forced Expiratory Volume in 1 second Area Under the Curve from 0 to 30 minutes Post-Exercise Challenge

LS mean change from baseline in post-exercise FEV_1 $AUC_{0\text{-}30min}$ was smaller with albuterol/budesonide (−36 mL) than with placebo (−317 mL), with a difference in LS means between the treatments of

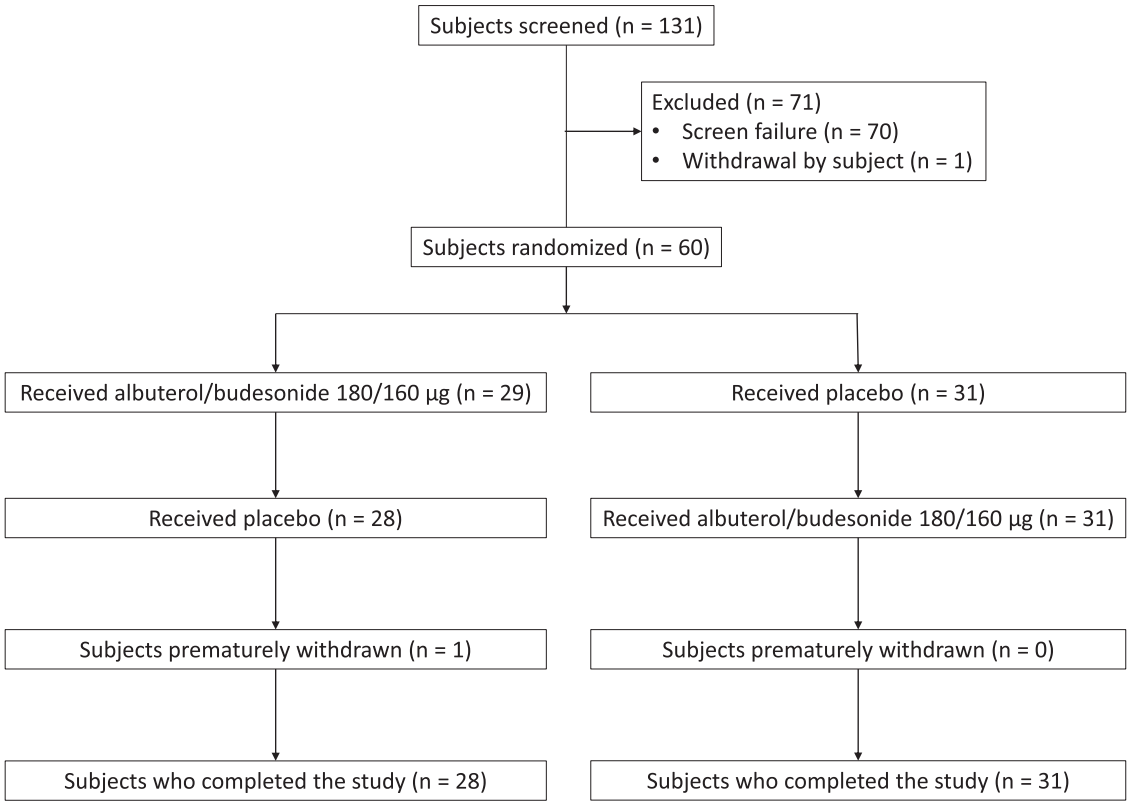

Figure 2. Subject disposition. Subjects who were screen failures did not meet inclusion/exclusion criteria. These included: unable to tolerate the lung function testing performed after ECT at Visit 1 or 2 without use of rescue medication (exclusion); EIB as defined by a ≥20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge at Visit 1 and at Visit 2 (inclusion); systemic corticosteroid use (any dosage and any indication) within 3 months before Visit 1 (exclusion); reveal acceptable spirometry performance (ie, meet ATS/ERS acceptability/repeatability criteria) (inclusion); willingness and ability to comply with all required study procedures including completion of all study visit assessments (inclusion); historical or current evidence of clinically significant disease including, but not limited to cardiovascular, hepatic, renal, hematological, neuropsychological, endocrine, gastrointestinal disorders (exclusion); receiving 1 of the following asthma therapies with stable dosing for at least the 4 weeks before Visit 1: as-needed SABA, or low-to-medium dose maintenance therapy with ICS and as-needed SABA (inclusion); each pre-exercise challenge (and pre-dose at Visits 2 and 3) best FEV_1 determination from the beginning of screening and before randomization ≥70% of predicted normal value (inclusion). ATS, American Thoracic Society; ECT, exercise challenge test; EIB, exercise-induced bronchoconstriction; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SABA, short-acting β_2-agonists.

Table 1
Subject Demographics

Characteristic	All subjects (N = 60)	Non-ICS background therapy (n = 31)	ICS background therapy (n = 29)
Age, y, mean (SD)	40.5 (11.76)	41.5 (13.29)	39.4 (10.00)
Sex, female (%)	63.3	58.1	69.0
Race (%)			
White	65.0	61.3	69.0
Black or African American	30.0	38.7	20.7
Asian	1.7	0.0	3.4
Native Hawaiian/other Pacific Islander	1.7	0.0	3.4
Other	1.7	0.0	3.4
BMI, kg/m^2, mean	28.8	28.5	29.1
Maximal HR at SV1, bpm, mean (SD)	165.6 (13.90)	165.8 (14.55)	165.4 (13.41)
Maximal HR at SV2, bpm, mean (SD)	164.8 (14.34)	163.9 (15.37)	165.7 (13.36)
5-min pre-ECT FEV_1 at SV1, % predicted, mean (SD)	83.11 (10.38)	81.64 (6.67)	84.67 (13.20)
Maximum % fall from 5-min pre-ECT FEV_1 at SV1, mean (SD)	27.10 (5.39)	27.53 (5.34)	26.64 (5.50)
Pre-dose, pre-ECT FEV_1 at SV2, % predicted, mean (SD)	82.75 (10.15)	81.24 (7.81)	84.37 (12.10)
Post-dose pre-ECT FEV_1 at SV2, % predicted, mean (SD)	82.89 (10.32)	81.84 (6.97)	84.01 (13.03)
Maximum % fall from post-dose pre-ECT FEV_1 at SV2, mean (SD)	28.31 (5.48)	28.55 (5.53)	28.05 (5.51)
Pre-dose, pre-ECT FEV_1 at randomization, L, mean (SD)	2.66 (0.61)	2.55 (0.54)	2.78 (0.67)
Pre-dose, pre-ECT FEV_1 at randomization, % predicted, mean (SD)	81.44 (10.59)	80.19 (6.66)	82.78 (13.61)
Pre-dose, pre-ECT FVC at randomization, L, mean (SD)	3.68 (1.02)	3.48 (0.90)	3.89 (1.11)
Pre-dose, pre-ECT FEV_1/FVC at randomization, %, mean (SD)	73.47 (8.69)	74.19 (7.76)	72.71 (9.67)

Abbreviations: BMI, body mass index; bpm, beats per minute; ECT, exercise challenge test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; ICS, inhaled corticosteroid; SV1, screening visit 1; SV2, screening visit 2.

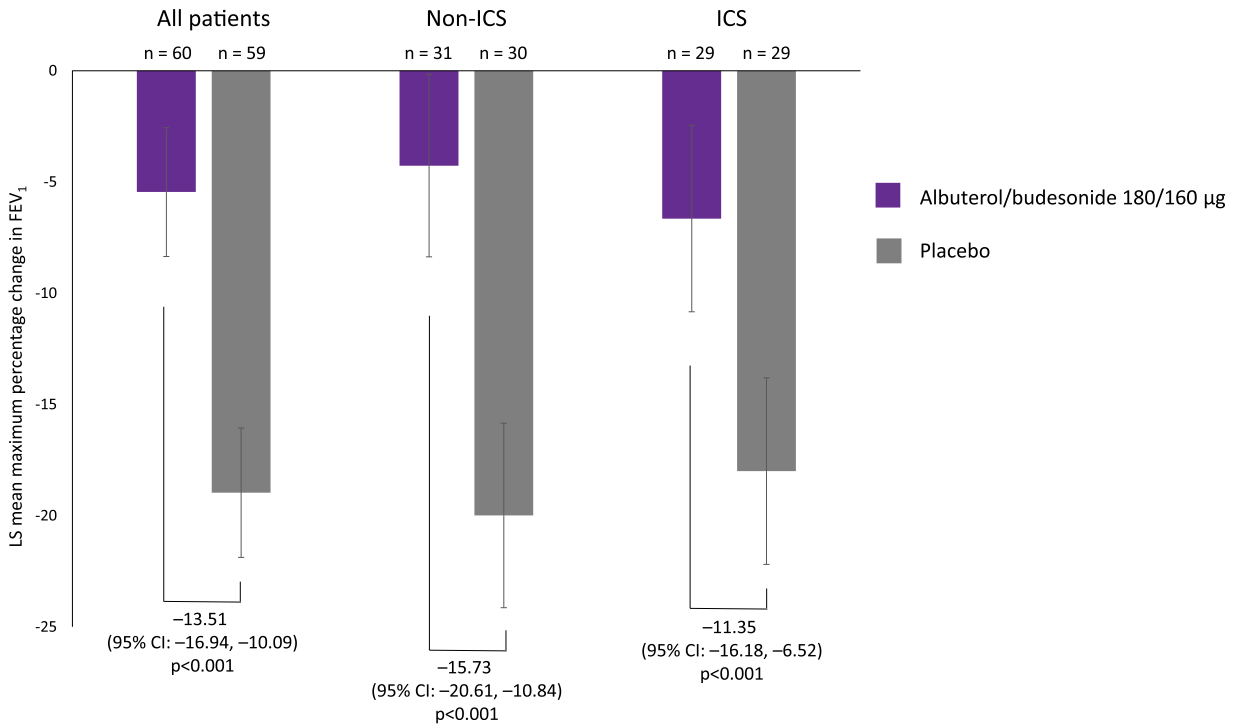

Figure 3. Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge. Error bars are 95% confidence intervals. FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LS, least squares.

281 mL (95% CI, 202-361; $P < .001$). In the non-ICS group, LS mean change in $AUC_{0\text{-}30min}$ with albuterol/budesonide was −23 mL compared with −332 mL with placebo. The difference between treatments was 309 mL (95% CI, 195−424; $P < .001$). In the ICS group, LS mean change in $AUC_{0\text{-}30min}$ was −49 mL with albuterol/budesonide and −302 mL with placebo. The difference between treatments was 253 mL (95% CI, 140−367; $P < .001$).

Safety

Two subjects in the placebo group experienced 1 mild AE each of dyspnea and anxiety; the latter was evaluated by the investigator to be related to the study drug. There were no AEs leading to death or discontinuation of treatment.

Discussion

In this first phase 3 study of albuterol/budesonide pMDI, a novel fixed-dose albuterol/ICS rescue medication, adolescents and adults with asthma and EIB who received a single dose of albuterol/budesonide 180/160 µg (2 inhalations of 90/80 µg) approximately 30 minutes before exercise had a significantly reduced maximum percentage fall from baseline in FEV_1 over 60 minutes post-exercise vs placebo pMDI. The mean maximum percentage fall in FEV_1 with albuterol/budesonide was more than 3-fold lower than that found with placebo. The treatment effect was consistent irrespective of whether subjects were receiving background ICS maintenance therapy or not —an important finding, as patients with asthma and EIB are often prescribed either SABA alone or low-to-medium dose ICS as maintenance therapy.[1]

All secondary and exploratory end points supported the results of the primary analysis, and a single dosage of albuterol/budesonide pMDI 180/160 µg was found to be well tolerated, with no safety concerns identified.

This study confirmed the efficacy of albuterol/budesonide in protecting against EIB. Thus, if patients with EIB and asthma were taking this combination for as-needed treatment of bronchoconstriction and prevention of exacerbations (currently in phase 3), it would also protect them against EIB. Combining the rapid bronchodilatory effects of a SABA with the anti-inflammatory properties of an ICS administered as-needed in a fixed-dose rescue medication has other potential benefits for patients with EIB and asthma; for example, ICS have previously been found to potentiate SABA-induced airway relaxation and lung function response in patients with asthma.[8,9] There are also potential nongenomic effects associated with ICS that could be of benefit in EIB, such as their ability to rapidly decrease airway mucosal blood flow and edema, potentiate the actions of bronchodilators, and modulate immune cell activity.[19,20]

For patients aged more than or equal to 12 years with mild persistent asthma, the National Asthma Education and Prevention Program 2020-focused updates recommend as-needed concomitant SABA and ICS as an alternative to daily low-dose ICS and as-needed SABA.[21] The 2 treatment options were found to have similar effects on asthma control, quality of life, and frequency of exacerbations when studied in large populations with similar safety profiles.[21]

A previous study (n = 66) revealed that an as-needed combination of ICS (budesonide) and formoterol was superior to as-needed SABA, both administered before exercise and for symptom relief at any time, in reducing EIB after 6 weeks of treatment in patients with mild asthma and EIB who were instructed to exercise 3 to 4 times per week.[22] The mean maximum post-exercise change in FEV_1 24 to 48 hours after the previous dose before exercise was −5.4% with as-needed budesonide-formoterol and +1.5% with as-needed SABA, representing a reduction of 28.5% and an increase of 8.9%, respectively.[22] Nevertheless, the benefits of adding ICS to SABA for EIB were not evaluated in the present study. In addition, the quoted trial used an active comparator, whereas the current study compared albuterol/budesonide with placebo.

The protection offered by albuterol/budesonide in this study in terms of magnitude of percentage fall from baseline in FEV_1, proportion of subjects protected, and time to recovery was similar to those in the pivotal trials for Proventil HFA (Merck Sharp & Dohme, New

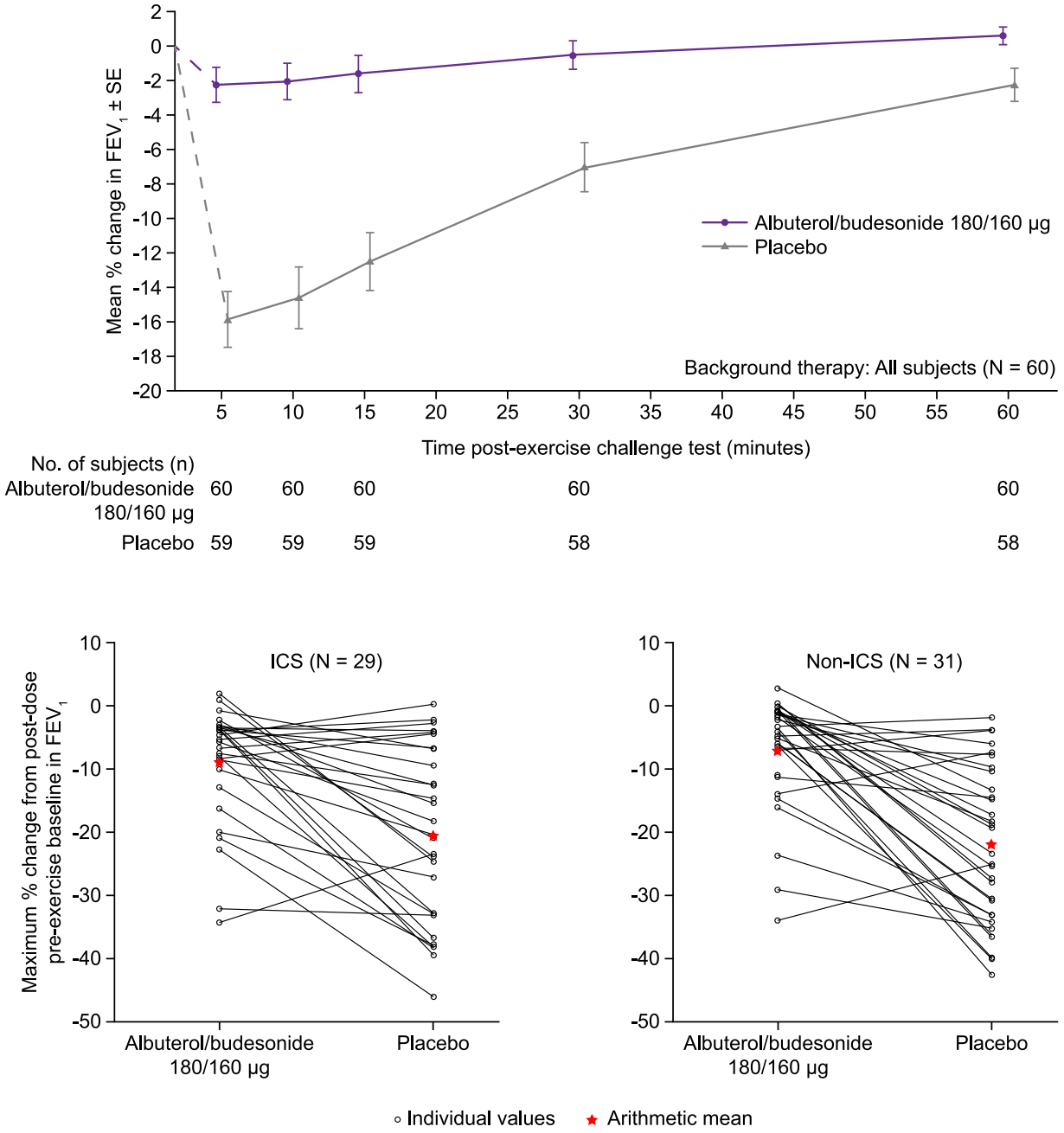

Figure 4. Mean percentage fall from post-dose pre-exercise baseline in FEV_1 by time point for (A) all subjects, (B) subjects on non-ICS background therapy, and (C) subjects on ICS background therapy. FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; pMDI, pressurized metered-dose inhaler; SE, standard error.

Jersey),[23] Ventolin HFA (GlaxoSmithKline, United Kingdom),[24] and ProAir Respiclick and HFA (Teva Pharmaceuticals, Israel).[15,25] All subjects in these trials had documented EIB and a history of asthma, except in the ProAir HFA study, which included subjects with or without asthma. Use of ICS background therapy was permitted in all trials except the Proventil HFA study.

For Proventil HFA 180 µg, the smallest mean change from pre-dose FEV_1 after exercise challenge was 2.0% compared with −23.7% for placebo (n = 20; difference, −25.7%; P <.001).[23] In a study of Ventolin HFA 180 µg vs placebo (n = 24), the mean maximum percentage falls in post-dose, pre-exercise FEV_1 post-exercise were 15.4% and 33.7%, respectively (difference, −17.3%; P <.001).[24] The efficacy of ProAir Respiclick pMDI 180 µg was superior to placebo pMDI in a single-dose, crossover study (n = 38),[15] where the mean maximum fall in post-dose, pre-exercise FEV_1 within 60 minutes post-exercise was 6.2% with Respiclick vs 22.4% with placebo (difference, −16.2% [95% CI, −20.2% to −12.1%]; P < .001).

In terms of protection against EIB, 5% (n = 1) in the Proventil HFA group had greater than or equal to 20% fall in FEV_1 compared with 60% (n = 12) in the placebo group (P < .001).[23] Treatment with Ventolin HFA resulted in a larger percentage of subjects partially protected (<20% maximum fall in FEV_1) post-exercise compared with placebo (61% vs 11%, respectively).[24] More Respiclick-treated subjects were fully protected (<10% maximum fall in FEV_1) against EIB vs placebo (84.2% vs 15.8%; OR, 28.4 [95% CI, 9.4-86.4]; P < .001), and median recovery time was 25.0 minutes quicker vs placebo (P < .001).[15] In a randomized, single-dose, crossover study of ProAir HFA 180 µg (n = 24), the percentage of subjects partially protected (<20% maximum fall in FEV_1) after exercise challenge was 83.3% (n = 20) vs 25.0% (n = 6) with placebo.[25]

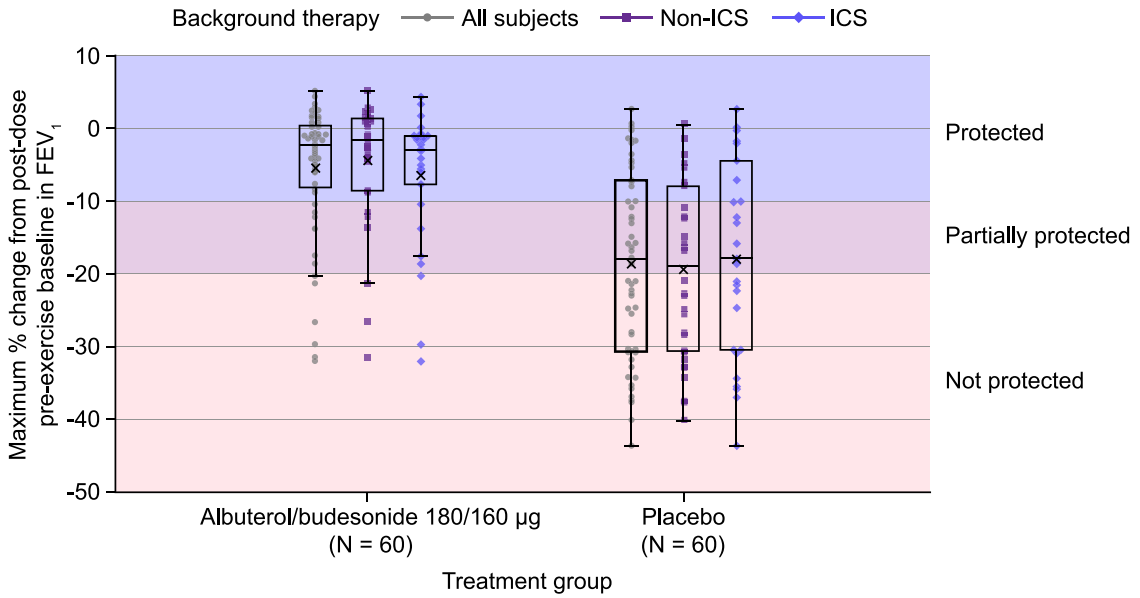

Figure 5. Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge. The box represents the interquartile range. The mean is plotted as an X within the box. The horizontal line in the box represents the median. The whiskers represent the maximum value within 1.5 times (interquartile range). All observations out of 1.5 times (interquartile range) are plotted individually. FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; pMDI, pressurized metered-dose inhaler.

In the present study with albuterol/budesonide, notably large placebo effects were observed in some subjects. One potential explanation is the phenomenon of patient expectancy, in which a subject's clinical response is related to their anticipated outcome. When EIB was confirmed by greater than or equal to 20% decrease in FEV_1 at SV2, the subjects were aware that they were receiving placebo, whereas at TV1 and TV2, the subjects knew that they might receive an active treatment. Thus, positive outcomes in the placebo group from screening to treatment visits might relate to the subjects' expected treatment benefit. This effect has previously been observed on both bronchoconstriction and bronchodilation responses in patients with asthma.[26-28]

A strength of the study was its multicenter, blinded, prospective design and the confirmation of effect with placebo at SV2. The inclusion of a placebo control group in the study design allows direct comparisons to the clinical trials of patients with asthma and EIB supporting other currently available albuterol products.[15,23-25] An albuterol-only treatment group was not included in this study, as the intention was to evaluate the efficacy and safety of albuterol/budesonide in preventing EIB, not to directly compare it with albuterol alone, which would have warranted a different study design. The requirement for no physical exercise in the 24 hours before study visits may be a limitation, as this is not necessarily representative of physically active behavior in patients with asthma and EIB. The study did not include patients with EIB without asthma, or patients with asthma treated with combination long-acting bronchodilators and ICS or EIB treated with leukotriene modifiers; however, the patient population included was similar to other studies of albuterol in EIB.[15,23-25]

The TYREE study revealed that albuterol/budesonide pMDI 180/160 µg (2 inhalations of 90/80 µg fixed-dosage combination of albuterol and budesonide) taken approximately 30 minutes before exercise significantly reduced the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed over 60 minutes post-exercise vs placebo pMDI in adolescents and adults with asthma and EIB. This albuterol/ICS rescue combination also increased the odds of being fully protected from EIB compared with placebo, revealed by maintaining FEV_1 within 90% of post-dose, pre-ECT baseline values over 60 minutes. These findings were consistent irrespective of subjects receiving background ICS maintenance therapy or as-needed SABA alone. Albuterol/budesonide pMDI 180/160 µg was well tolerated.

Albuterol/budesonide pMDI is being developed as a potential novel albuterol/ICS rescue medication for patients with asthma to treat bronchoconstriction and reduce the risk of severe exacerbations. The TYREE study suggests that, should albuterol/budesonide pMDI become available as a rescue treatment for asthma, this novel therapy could also be effective for the prevention of EIB.

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