Albuterol-budesonide rescue reduces progression from asthma deterioration to severe exacerbation

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Clinical Implications

During an asthma deterioration, patients experience increased symptoms and use more rescue inhaler. By using an albuterol-budesonide inhaler for rescue, patients receive more anti-inflammatory therapy when most needed, reducing the risk of a deterioration progressing to a severe exacerbation.

Patients with all asthma severities and levels of control are susceptible to exacerbations, even those with high adherence to maintenance therapy.[1] Before an asthma exacerbation, symptoms and short-acting β_2-agonist (SABA) rescue use increase and peak expiratory flow decreases.[2] This provides a "window of opportunity" to potentially prevent exacerbation occurrence and avoid systemic corticosteroids (SCS) by treating symptoms and inflammation concomitantly with an inhaled corticosteroid (ICS) and fast-acting bronchodilator, as advocated by the Global Initiative for Asthma (GINA), the National Asthma Education and Prevention Program (NAEPP), and the European Respiratory Society (ERS).[3-5] Although GINA, NAEPP, and ERS include ICS-formoterol in their recommendations for both maintenance therapy and as rescue for many patients, no ICS-formoterol product is approved by the US Food & Drug Administration (FDA) for use in this manner.

Albuterol-budesonide 180/160 μg pressurized metered-dose inhaler (pMDI) was approved in 2023 by the US FDA for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations for patients with asthma 18 years and older.[6] SABA-ICS was subsequently included in the GINA 2023 report as an alternative rescue option at all therapy steps for patients 12 years or older.[4]

MANDALA was a phase 3, randomized, double-blind trial, which demonstrated that as-needed albuterol-budesonide 180/160 μg pMDI significantly reduced severe exacerbation risk by 27% and mean annualized total SCS exposure by 33% versus as-needed albuterol 180 μg in patients 12 years or older with uncontrolled moderate-to-severe asthma receiving ICS-containing maintenance therapies.[7] This prespecified exploratory analysis of MANDALA evaluated asthma deteriorations and the effect of as-needed albuterol-budesonide on progression from deterioration to a severe exacerbation.

The MANDALA study design (NCT03769090) has been described previously.[7] In brief, exacerbation risk over ≥24 weeks was assessed with albuterol-budesonide pMDI (180/160 μg or 180/80 μg) versus albuterol 180 μg in symptomatic patients with a history of 1 or more severe exacerbations. A deterioration was defined as 1 or more of the following for ≥2 consecutive days: (1) ≥20% decline from baseline in peak expiratory flow; (2) >4 inhalations/d of study medication (and ≥2 times as frequent vs baseline; 1 dose = 2 inhalations); (3) nighttime symptom score ≥2 and increased from baseline, or daytime symptom score of 3 and increased from baseline (Table I). Study medication use was documented by patients each morning and evening in an electronic diary. Patients with a first postrandomization asthma deterioration were analyzed to evaluate progression within the subsequent 21 days to a severe exacerbation (defined as asthma worsening requiring ≥3 days of SCS, an emergency department visit leading to ≥3 days of SCS use, asthma-related hospitalization for ≥24 hours, or asthma-related death). As events of worsening occurred after randomization, baseline demographic/clinical characteristics were compared between the treatment groups to evaluate the likelihood of material bias impacting the analysis.

Time to first severe exacerbation from first postrandomization deterioration was analyzed using a Cox proportional hazards model adjusted for treatment, age group, region, and number of severe exacerbations in the previous year. Treatments were compared by estimating the hazard ratio (HR), corresponding 95% confidence interval (CI), and 2-sided P value. Data are presented for the prespecified analysis of albuterol-budesonide 180/160 μg and 180/80 μg versus albuterol 180 μg in patients 12 years or older (primary efficacy population). A *post hoc* analysis evaluated albuterol-budesonide 180/160 μg in patients 18 years or older (FDA-approved population). No adjustments were made for type I error; P values <.05 were considered significant. Further *post hoc* analyses were conducted to assess study medication use at the time of first deterioration for subgroups of patients who progressed to a severe exacerbation within the next 21 days and those who did not (patients who met the definition of deterioration solely on criterion 2 [increased study medication use] were excluded from these *post hoc* analyses).

A total of 3040 patients 12 years or older were randomized. Baseline demographic and clinical characteristics were generally similar between the treatment groups, overall, and in patients with an asthma deterioration (Table I). A deterioration was experienced by 747 (73.7%) patients receiving albuterol-budesonide 180/160 μg, 729 (72.0%) receiving albuterol-budesonide 180/80 μg, and 805 (79.4%) receiving albuterol: 180/160 μg versus albuterol (HR: 0.83; 95% CI: 0.75, 0.92; $P < .001$); 180/80 μg versus albuterol (HR: 0.81; 95% CI: 0.73, 0.90; $P < .001$). Results were similar for patients 18 years or older (180/160 μg vs albuterol: 74.1% vs 79.6%; HR: 0.83; 95% CI: 0.75, 0.92; $P < .001$).

In patients 12 years or older, the risk of progression from deterioration to severe exacerbation was reduced by 41% with albuterol-budesonide 180/160 μg (HR: 0.59; 95% CI: 0.41, 0.84; $P = .004$) and 22% with albuterol-budesonide 180/80 μg (HR: 0.78; 95% CI: 0.56, 1.09; $P = .142$) versus albuterol

TABLE I. Baseline demographics and clinical characteristics for the overall patient population and for the subset of patients with an asthma deterioration (patients 12 years or older)*

	All patients			Patients with an asthma deterioration		
Characteristic	Albuterol-budesonide 180/160 μg (N = 1013)	Albuterol-budesonide 180/80 μg (N = 1013)	Albuterol 180 μg (N = 1014)	Albuterol-budesonide 180/160 μg (N = 747)	Albuterol-budesonide 180/80 μg (N = 729)	Albuterol 180 μg (N = 805)
Age (y), mean (SD)	50.6 (15.1)	50.1 (15.0)	50.7 (15.5)	51.0 (14.6)	50.5 (14.7)	51.0 (15.4)
Age groups (y), n (%)						
≥12 to <18	34 (3.4)	32 (3.2)	34 (3.4)	22 (2.9)	21 (2.9)	25 (3.1)
≥18 to <65	787 (77.7)	804 (79.4)	783 (77.2)	586 (78.4)	580 (79.6)	627 (77.9)
≥65	192 (19.0)	177 (17.5)	197 (19.4)	139 (18.6)	128 (17.6)	153 (19.0)
Female sex, n (%)	645 (63.7)	671 (66.2)	681 (67.2)	493 (66.0)	500 (68.6)	547 (68.0)
Prebronchodilator FEV_1 % predicted normal, mean (SD)	68.2 (16.0)	67.7 (16.1)	68.7 (15.7)	67.5 (15.9)	66.3 (16.2)	68.0 (15.7)
Maintenance treatment, n (%)†						
Low-dose ICS-LABA or medium-dose ICS	314 (31.0)	325 (32.1)	295 (29.1)	217 (29.0)	230 (31.6)	246 (30.6)
Medium-dose ICS-LABA or high-dose ICS	385 (38.0)	414 (40.9)	421 (41.5)	289 (38.7)	308 (42.2)	333 (41.4)
High-dose ICS-LABA	295 (29.1)	257 (25.4)	276 (27.2)	228 (30.5)	178 (24.4)	209 (26.0)
ACQ-5 score, mean (SD)	2.6 (0.7)	2.6 (0.7)	2.6 (0.6)	2.7 (0.7)	2.7 (0.7)	2.6 (0.7)
No. of severe exacerbations in the prior year, n (%)						
1	788 (77.8)	795 (78.5)	808 (79.7)	553 (74.0)	554 (76.0)	630 (78.3)
>1	225 (22.2)	218 (21.5)	206 (20.3)	194 (26.0)	175 (24.0)	175 (21.7)
Symptom score, mean (SD)‡,§						
Nighttime score	0.9 (0.6)	0.9 (0.7)	0.9 (0.7)	1.0 (0.6)	1.0 (0.6)	1.0 (0.6)
Daytime score	1.1 (0.6)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
PEF (L/min), mean (SD)‡						
Morning	298.1 (114.0)	296.7 (106.9)	293.4 (108.9)	286.9 (109.8)	284.3 (102.7)	287.1 (103.6)
Evening	310.4 (116.4)	307.2 (107.9)	306.1 (110.9)	299.0 (112.1)	294.1 (104.8)	300.7 (105.1)
SABA use (no. of inhalations/d), mean (SD)‡	3.4 (2.2)	3.4 (2.2)	3.3 (2.2)	3.5 (2.2)	3.7 (2.2)	3.4 (2.2)

ACQ-5, 5-item Asthma Control Questionnaire; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *PEF*, peak expiratory flow; *SABA*, short-acting β_2 agonist; *SD*, standard deviation.

*Full analysis set, patients aged 12 years or older; demographics for the population 18 years or older can be found in the AIRSUPRA Prescribing Information.

†Maintenance treatment categories correspond to steps 3, 4, and 5 in the Global Initiative for Asthma 2023 report.[4]

‡Baseline is defined as the average score over the last 10 days of the run-in period.

§Symptom score is assessed on a 4-point scale. For nighttime: 0 (no asthma symptoms), 1 (you were aware of your asthma symptoms but you can easily tolerate the symptoms), 2 (your asthma was causing you enough discomfort to cause problem with sleep), and 3 (you were unable to sleep because of your asthma). For daytime: 0 (no asthma symptoms), 1 (you were aware of your asthma symptoms but you can easily tolerate the symptoms), 2 (your asthma was causing you enough discomfort to cause problem with normal activities), and 3 (you were unable to do your normal activities because of your asthma).

(Figure 1). Results were similar for patients 18 years or older (180/160 μg vs albuterol: HR: 0.60; 95% CI: 0.42, 0.87; $P = .007$; Figure 1).

Over the course of the study, the mean as-needed use of study medication was 2.6, 2.7, and 2.8 inhalations/d in the albuterol-budesonide 180/160 μg, albuterol-budesonide 180/80 μg, and albuterol groups, respectively (in patients 18 years or older). *Post hoc* analysis showed that this increased around the time of a deterioration (modified definition) in both treatment arms, with the increase numerically greater in those who went on to experience a severe exacerbation in the next 21 days: at the onset of deterioration, the mean daily as-needed use of study medication increased to 3.8, 3.9, and 4.5 inhalations of albuterol-budesonide 180/160 μg, albuterol-budesonide 180/80 μg, and albuterol, respectively, among patients who progressed to a severe exacerbation, and to 3.3, 3.5, and 3.4 inhalations, respectively, in patients who did not progress to a severe exacerbation (data for patients 18 years or older).

In this analysis, as-needed albuterol-budesonide 180/160 μg and 180/80 μg resulted in significantly fewer deteriorations versus albuterol in patients receiving ICS-containing maintenance. Moreover, among patients who experienced a deterioration, the risk of the deterioration progressing to severe exacerbation within 21 days was significantly reduced for patients receiving albuterol-budesonide 180/160 μg versus albuterol, suggesting that the effect of albuterol-budesonide 180/160 μg is

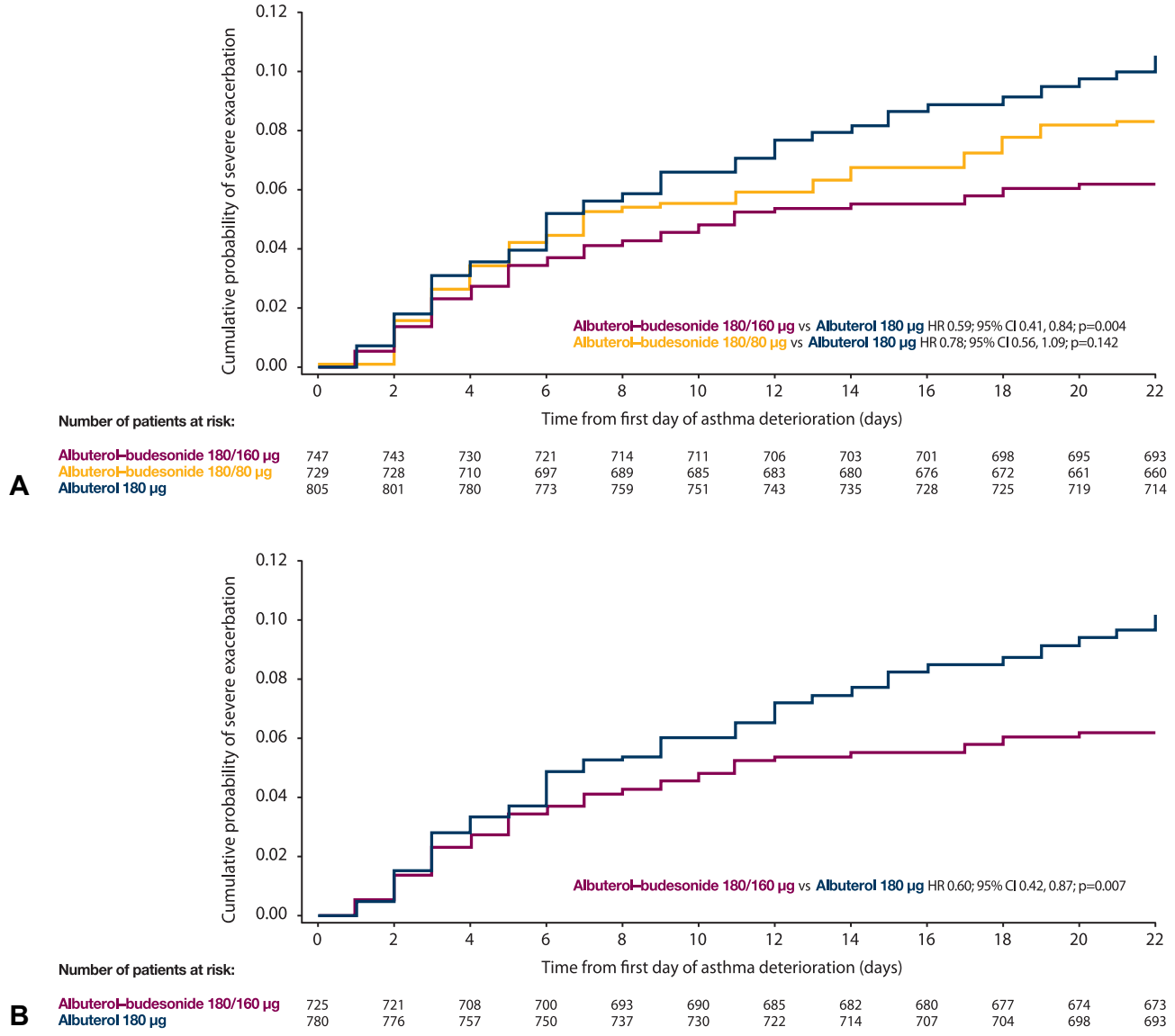

FIGURE 1. Time to first severe exacerbation after a deterioration in (**A**) patients aged 12 years or older and in (**B**) a *post hoc* analysis of patient aged 18 years or older. A deterioration was defined as 1 or more of the following for ≥2 consecutive days: peak expiratory flow: decline ≥20% from baseline; study medication use: >4 inhalations/d and ≥2 times as frequently as at baseline (1 dose = 2 inhalations); symptoms: nighttime score >baseline and ≥2, or daytime score >baseline and equal to 3. A severe exacerbation was defined as an asthma worsening leading to 1 or more of the following: ≥3-day course of SCS or the corresponding single injectable dose; emergency department or urgent care visit due to asthma that required SCS; hospitalization due to asthma; and death due to asthma. Among patients aged 12 years or older with a deterioration, 46 (6.2%) receiving albuterol-budesonide 180/160 µg, 59 (8.1%) receiving albuterol-budesonide 180/80 µg, and 83 (10.3%) receiving albuterol progressed to a severe exacerbation within 21 days. Among patients aged 18 years or older with a deterioration, 45 (6.2%) receiving albuterol-budesonide 180/160 µg and 79 (10.1%) receiving albuterol progressed to a severe exacerbation within 21 days. *CI*, Confidence interval; *HR*, hazard ratio; *SCS*, systemic corticosteroids.

not only related to reducing deteriorations but also due to altering their progression to severe exacerbation. This suggests a "window of opportunity" to treat symptoms and inflammation concomitantly to reduce the risk of further progression to a severe exacerbation. In mild asthma, as-needed budesonide-formoterol was shown to reduce the short-term risk of severe exacerbations versus SABA after a single day of higher use, even when overall use was infrequent.[8] Treating asthma symptoms and inflammation concomitantly with a rapid-acting bronchodilator and anti-inflammatory in a single inhaler aligns with patient behavior to prioritize quick relief when needed; patients get more ICS when they need it simply by using their rescue inhaler in response to symptoms.[9]

This study demonstrates that as-needed albuterol-budesonide 180/160 µg reduces progression to a severe asthma exacerbation in patients receiving a wide range of ICS-containing maintenance,

including those on an alternative (nonbudesonide) ICS alone or alternative ICS combined with formoterol or nonformoterol long-acting β_2-agonist (LABA) (with or without another controller). This enhances the generalizability of the findings to all ICS and combination ICS/LABA medications for the treatment of moderate-to-severe asthma.

The study did not examine the reason why some patients progress from an asthma deterioration to a severe exacerbation. The reduction in risk of progression from deterioration to severe exacerbation versus albuterol was almost 2-fold greater with the albuterol-budesonide 180/160 μg dose than the 180/80 μg dose, highlighting the central role of inflammation in driving this progression and the need to address this with an anti-inflammatory rescue. Many factors contribute to exacerbations, not all of which may fully respond to appropriately timed administration of additional ICS, for example, those caused by triggers that do not elicit a true inflammatory response, poor inhaler technique, and other overlapping medical conditions that may present in a similar way as an acute asthma exacerbation (eg, vocal cord dysfunction, a severe exacerbation due to chronic obstructive pulmonary disease [COPD], or bronchiectasis requiring antibiotics rather than SCS). COPD or other significant lung diseases were listed as exclusion criteria in MANDALA and therefore unlikely to be a reason in this case, and patients had to demonstrate an acceptable pMDI administration technique to be eligible for participation; however, during times of acute symptoms or airway obstruction, their technique may not be adequate.

These data are from a clinical trial in patients with uncontrolled moderate-to-severe asthma who were adherent to their ICS-containing maintenance on a median of 85% of study days; results may not be the same with lower levels of maintenance adherence. The time-to-event analysis is based on the subgroup of patients experiencing an asthma deterioration after randomization; therefore, subgroup selection may be influenced by the assigned treatment, potentially introducing bias to the estimated treatment effects. However, the evaluation of baseline demographic and clinical characteristics found no meaningful differences between the treatment groups; differences in other characteristics/factors cannot be ruled out. Finally, other indicators of a deterioration may exist that are not captured in the current definition.

In conclusion, as-needed albuterol-budesonide 180/160 μg significantly reduced the risk of asthma deteriorations and further progression from an asthma deterioration to severe exacerbation compared with albuterol 180 μg, highlighting the importance of treating both inflammation and symptoms concomitantly.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The MANDALA study was approved by the relevant ethics committee or institutional review board at each site. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Written informed consent was obtained from each patient (or legal guardian) before any study-related procedures.

DATA AVAILABILITY

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

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