Ann Allergy Asthma Immunol 136 (2026) 54–60

Contents lists available at ScienceDirect

Original Article

Albuterol–budesonide rescue inhaler for asthma

Patterns of use and safety in the MANDALA trial

Bradley E. Chipps, MD[*]; Reynold A. Panettieri, Jr MD[†,‡]; Neil Skolnik, MD[§,‖]; Christy Cappelletti, PharmD[¶]; Sami Z. Daoud, MD[#]; Lynn Dunsire, MSc[¶]; Ileen A. Gilbert, MD[**]; Alberto Papi, MD[††]

[*] *Capital Allergy & Respiratory Disease Center, Sacramento, California*
[†] *Rutgers Institute for Translational Medicine and Science, The State University of New Jersey, New Brunswick, New Jersey*
[‡] *Child Health Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, New Jersey*
[§] *Abington Family Medicine, Jenkintown, Pennsylvania*
[‖] *Department of Family and Community Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania*
[¶] *BioPharmaceuticals R&D, AstraZeneca, Durham, North Carolina*
[#] *BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland*
[**] *BioPharmaceuticals, US Medical, AstraZeneca, Wilmington, Delaware*
[††] *Department of Respiratory Medicine, University of Ferrara Medical School, Ferrara, Italy*

ARTICLE INFO

Article history:
Received for publication March 13, 2025.
Received in revised form July 8, 2025.
Accepted for publication July 9, 2025.

ABSTRACT

Background: The MANDALA study (NCT03769090) in moderate-to-severe asthma served as the basis of the Food and Drug Administration's 2023 approval of albuterol–budesonide 180/160 μg pressurized metered-dose inhaler for the as-needed treatment or prevention of bronchoconstriction and to reduce exacerbation risk in patients with asthma aged 18 years or older. Clinicians would benefit from an understanding of the patterns of use of albuterol–budesonide vs albuterol and overall inhaled corticosteroid (ICS) exposure when ICS-containing rescue therapies are used alongside ICS-based maintenance therapies.
Objective: To evaluate patterns of as-needed use and safety profiles of albuterol–budesonide 180/160 μg vs albuterol 180 μg, using data from MANDALA.
Methods: Study medication use was patient-documented using an electronic diary. Safety was assessed as adverse events. Patterns of study medication use (2 inhalations = 1 dose) were summarized as mean percentages of days in which inhalations per day fell within predefined categories (0, 1-2, 3-4, 5-6, 7-8, 9-10, 11-12, and >12).
Results: The safety population included 981 patients randomized to as-needed albuterol–budesonide and 981 to as-needed albuterol. Patients adhered to maintenance therapy regimens on a mean of more than or equal to 75% of days. Use of as-needed study drug was similar in both groups (mean of 2.6 and 2.8 inhalations/d of albuterol–budesonide and albuterol, respectively). High daily use (≥8 inhalations/d) or long-term high daily use (≥7 consecutive days) was rare. Adverse event frequencies (ICS-associated and not) were low and comparable between groups, regardless of mean daily as-needed use.
Conclusion: Patterns of use and safety profiles were similar between as-needed albuterol–budesonide and albuterol.
Trial Registration: ClinicalTrials.gov Identifier: NCT03769090.
© 2025 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

In 2021, approximately 10 million of the nearly 25 million people with asthma in the United States reported 1 or more asthma exacerbations, with approximately 1 million reporting asthma-related emergency department visits.[1] These exacerbations contribute to significant morbidity and mortality, and their prevention is imperative in the management of asthma.[2-4] Preventing severe exacerbations also reduces patient exposure to systemic corticosteroids (SCSs) required for their treatment but which, over

The affiliation of Dr Cappelletti was at the time of the study.
Disclaimer: Prior presentation: Presented in part at the European Respiratory Society International Congress, Milan, Italy, September 9 to 13, 2023, and the American College of Allergy, Asthma & Immunology Annual Scientific Meeting, Anaheim, California, November 9 to 13, 2023.
Address correspondence to: Ileen A. Gilbert, MD, BioPharmaceuticals, US Medical, AstraZeneca, 1800 Concord Pike, Wilmington, DE 19803 E-mail: ileen.gilbert@astrazeneca.com.

https://doi.org/10.1016/j.anai.2025.07.008
1081-1206/© 2025 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

time, can result in chronic adverse health conditions.[5,6] Recently, a call for SCS stewardship in asthma has been raised, due to the understanding that as few as 4 to 6 courses (500-1000 mg prednisolone) in a lifetime increases the risk of developing illnesses, such as osteoporosis, hyperglycemia, cardiovascular disease, and psychiatric disturbances.[7]

Airway inflammation varies over time and in intensity in patients with asthma.[4,8] In the days preceding an exacerbation, patients experiencing symptoms increase the use of their rescue inhaler to achieve quick relief.[9-13] However, short-acting β_2-agonist (SABA) rescue therapy alone does not treat underlying and fluctuating airway inflammation, leaving patients at risk of an exacerbation.[14,15] Furthermore, increased use of SABA rescue therapy is predictive of upcoming severe exacerbations requiring treatment with SCS.[11,15-20]

To ensure patients with asthma receive the anti-inflammatory therapy needed to reduce exacerbation risk at the time of an asthma worsening, both the National Asthma Education and Prevention Program guidelines and the Global Initiative for Asthma (GINA) report state that the concomitant use of a fast-acting bronchodilator and inhaled corticosteroid (ICS) is preferred over SABA alone as rescue therapy.[4,21]

A combination of SABA–ICS, albuterol–budesonide 180/160 μg pressurized metered-dose inhaler (pMDI), was approved by the US Food and Drug Administration (FDA) in 2023 for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.[22] This approval was based primarily on results from the MANDALA study, a large, phase 3, randomized, double-blind trial, which demonstrated as-needed albuterol–budesonide 180/160 μg pMDI significantly reduced the risk of a severe exacerbation by 28% and mean annualized total SCS exposure by 32%, vs as-needed albuterol 180 μg, in patients aged 18 years or older with uncontrolled moderate-to-severe asthma receiving a range of ICS-containing maintenance therapies (GINA steps 3-5).[4,5,23] Here, data from MANDALA were evaluated to determine the patterns of use and safety profile of albuterol–budesonide, compared with albuterol, overall and based on the amount of study medication used and the dose of ICS maintenance therapy prescribed.

Methods

The MANDALA study design (NCT03769090) has been described previously.[5] The study was approved by the appropriate institutional and national regulatory authorities and ethics committees, and all patients or their guardians provided written informed consent.[5] In brief, MANDALA evaluated the efficacy and safety of as-needed albuterol–budesonide (180/160 μg and 180/80 μg), compared with those of albuterol 180 μg, in symptomatic patients (aged ≥4 years) with moderate-to-severe asthma who had experienced 1 or more severe exacerbations in the previous 12 months. These patients received a medium-to-high dose of ICS or a low-to-high dose of ICS–long-acting β_2-agonist combination (defined as GINA 2023 treatment steps 3-5[24]), with or without another controller, for 3 or more months, with stable dosing for 4 or more weeks before screening. Patients continued to use their own maintenance medications throughout the trial.

Patients aged 12 years or older were randomized 1:1:1 to as-needed albuterol–budesonide pMDI 180/160 μg or 180/80 μg or albuterol 180 μg for a minimum of 24 weeks; patients aged 4 to 11 years were randomized 1:1 to receive as-needed albuterol–budesonide 180/80 μg pMDI or albuterol 180 μg. Data are presented here for albuterol–budesonide 180/160 μg (the FDA-approved dose) vs albuterol 180 μg for the subgroup of patients aged 18 years or older (the FDA-approved age range).[22] Each dose of rescue albuterol–budesonide 180/160 μg comprised 2 actuations of 90 μg albuterol and 80 μg budesonide; each dose of albuterol 180 μg comprised 2 actuations of 90 μg albuterol. Study medications were delivered through pMDIs; patients were instructed to use 2 inhalations as needed, in response to symptoms, before exercise, and as they would normally use their current albuterol therapy, with the maximum daily dose of study medication being 12 inhalations (6 doses). Patients were not permitted to use other rescue medications. Study medication use was documented by patients each morning and evening in an electronic diary.

Safety was evaluated based on adverse events (AEs) and serious AEs (SAEs), according to preferred terms in the Medical Dictionary for Regulatory Activities version 24.0 and was assessed from receipt of written informed consent to the end of the safety follow-up period (2 weeks after the last in-clinic visit). Local and systemic ICS-associated AEs were defined a priori (eMethods).

Statistical Analyses

During the randomized treatment period, patterns of study medication use were summarized *post hoc* according to the mean percentage of days when the number of rescue medication inhalations per day fell within the following categories: 0, 1 to 2, 3 to 4, 5 to 6, 7 to 8, 9 to 10, 11 to 12, or more than 12 (corresponding to the following doses per day categories: 0, 0.5 to 1, 1.5 to 2, 2.5 to 3, 3.5 to 4, 4.5 to 5, 5.5 to 6, or more than 6). Summary statistics were calculated for patients with study medication use of 2 full doses a day or more: 4 or more, 8 or more, or 12 or more inhalations/d and were grouped by whether these thresholds were met on 1 or more occasion, or 2 or more, 7 or more, or 14 or more consecutive days. Patterns of use were evaluated for a subset of the full analysis set, comprising all patients aged 18 years or older who had been randomized to the albuterol–budesonide 180/160 μg or albuterol 180 μg groups and received any amount of study medication. Results were classified according to the assigned study medication.

AEs were summarized, overall and for subgroups, by mean inhalations of the rescue medication per day (>0-<3, 3-<6, and ≥6 [corresponding to doses per day of >0-<1.5, 1.5-<3, and ≥3]) and by ICS maintenance therapy daily dose at baseline (low, medium, or high, per GINA 2020[25]; eTable 1). Safety analyses were conducted in a subset of the safety population, which included all patients aged 18 years or older in the albuterol–budesonide 180/160 μg or albuterol 180 μg groups who had received any amount of study medication, classified according to study medication received.

Results

The safety population included 981 patients randomized to albuterol–budesonide 180/160 μg and 981 to albuterol 180 μg; the full analysis set included 979 and 980 patients, respectively. Patient demographics and clinical characteristics for the full analysis set are found in Table 1. In brief, 389 patients were 65 years of age or older; 23%, 46%, and 31% of patients were on low-, medium-, and high-dose ICS-based maintenance therapy, respectively.

Mean (SD) duration of exposure was 313.6 (131.8) days per patient for albuterol–budesonide and 304.3 (133.3) days per patient for albuterol; total duration of treatment across all patients (number of years of treatment for each patient multiplied by total number of patients) was 842.4 and 817.4 patient-years, respectively. During the trial, patients reported taking their maintenance medication on a mean (SD) of 75.1% (25.4%) and 76.1% (25.0%) of days in the albuterol–budesonide and albuterol groups, respectively.

Table 1
Patient Demographics and Clinical Characteristics at Baseline[a]

Characteristic	Albuterol–budesonide 180/160 μg[b] (n = 979)	Albuterol 180 μg (n = 980)
Age, y, mean (SD)	51.9 (13.7)	52.0 (14.2)
Age distribution, n (%)		
18-64 y	787 (80.4)	783 (79.9)
≥65 y	192 (19.6)	197 (20.1)
Female biologic sex, n (%)	631 (64.5)	662 (67.6)
Race or ethnic group, n (%)		
White	800 (81.7)	824 (84.1)
Black	129 (13.2)	112 (11.4)
Asian	26 (2.7)	20 (2.0)
American Indian or Alaska Native	1 (0.1)	0 (0)
Other	23 (2.3)	24 (2.4)
Ethnicity, n (%)		
Hispanic or Latino	221 (22.6)	284 (29.0)
Geographic region, n (%)		
North America, Western Europe, and South Africa	511 (52.2)	513 (52.3)
Rest of world	468 (47.8)	467 (47.7)
Pre-bronchodilator FEV_1		
Volume, L, mean (SD)	2.0 (0.7)	2.0 (0.7)
Percent predicted normal, %, mean (SD)	67.7 (15.9)	68.3 (15.5)
Reversibility in FEV_1, %, mean (SD)	27.5 (15.4)	27.91 (15.7)
Maintenance treatment, n (%)		
Low-dose ICS-LABA or medium-dose ICS	301 (30.7)	284 (29.0)
Medium-dose ICS-LABA or high-dose ICS	373 (38.1)	406 (41.4)
High-dose ICS-LABA	289 (29.5)	272 (27.8)
Severe asthma exacerbations in the 12 mo before screening, n (%)		
1	766 (78.2)	784 (80.0)
2	173 (17.7)	146 (14.9)
3	27 (2.8)	43 (4.4)
≥4	13 (1.3)	7 (0.7)
ACQ-5 score, mean (SD)[b]	2.6 (0.7)	2.6 (0.6)
SABA use, number of inhalations per day, mean (SD)[b]	3.4 (2.2)	3.3 (2.2)

Abbreviations: ACQ-5, Asthma Control Questionnaire; FDA, Food and Drug Administration; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting ß$_2$-agonist; SABA, short-acting ß$_2$-agonist.
NOTE. Full analysis set, subset of patients aged 18 years or older randomized to albuterol–budesonide 180/160 μg or albuterol 180 μg.
[a]Baseline is defined as the last non-missing overall score, taken before and including randomization.
[b]Patients randomized to albuterol–budesonide 180/80 μg were not included in this analysis, which focused on the FDA-approved dose of albuterol–budesonide 180/160 μg.

Patterns of As-Needed Use

During the trial, patients used a mean (SD) of 2.6 (1.9) inhalations per day of albuterol–budesonide and 2.8 (1.9) of albuterol, representing approximately 1.3 and 1.4 uses of rescue therapy per day, respectively; patterns of as-needed use were similar in both treatment groups (Fig 1). The median number of inhalations per day was 2.3 in the albuterol–budesonide group and 2.5 in the albuterol group.

Patients in the albuterol–budesonide and albuterol groups used 0 inhalations of as-needed study medication on 24% and 20% of days, 1 to 2 inhalations on 30% of days each, and 4 or fewer inhalations on 85% and 83% of days, respectively (Fig 1). As-needed use of 9 or more inhalations/d was uncommon, with both treatment groups using 9 or more inhalations on less than 2% of days (Fig 1). High as-needed use for long periods was also uncommon; only 5% of patients used 8 or more inhalations on 7 or more consecutive days and only 3% used 8 or more inhalations on 14 or more consecutive days in each treatment group (Fig 2).

Overview of Safety

AE frequencies were similar between the albuterol–budesonide 180/160 μg and albuterol 180 μg treatment groups, and discontinuations due to AEs were low (≤1% in each group; Table 2). The more common all-cause AEs in both treatment groups were nasopharyngitis, headache, COVID-19, and upper respiratory tract infections (Table 2). Compared with the overall population (all patients aged 18 years or older) in each treatment group, no clinically important differences were observed in the frequency of AEs or SAEs in patients aged 65 years or older (eTable 2). Pneumonia was reported as an AE by a numerically greater proportion of patients in the albuterol–budesonide group than the albuterol group overall (15 [1.5%] vs 6 [0.6%] patients) and among patients aged 65 years or older (6 [3.1%] vs 2 [1.0%] patients).

Inhaled Corticosteroid–Associated Adverse Events

The frequencies of local and systemic ICS-associated AEs were low and generally comparable between treatment groups (Table 3). Frequencies of oral candidiasis and oropharyngeal candidiasis were numerically higher in patients receiving albuterol–budesonide vs albuterol (oral candidiasis, 1.0% vs 0.4%; oropharyngeal candidiasis, 0.3% vs 0.1%; Table 3).

Safety by Mean Daily As-Needed Use of Study Medication

Treatment groups had comparable frequencies of AEs, regardless of mean daily as-needed study medication use (Table 4). Nasopharyngitis, headache, and COVID-19 were the more frequently reported AEs in the albuterol–budesonide group at mean daily study medication uses of more than 0 to less than 3 or 3 to less than 6 inhalations/d (eFig 1). The minimal percentage of patients (<5%) who used a mean of 6 or more inhalations/d of albuterol–budesonide had comparable incidences of AEs vs patients using equivalent inhalations of albuterol (Table 4 and eFig 1).

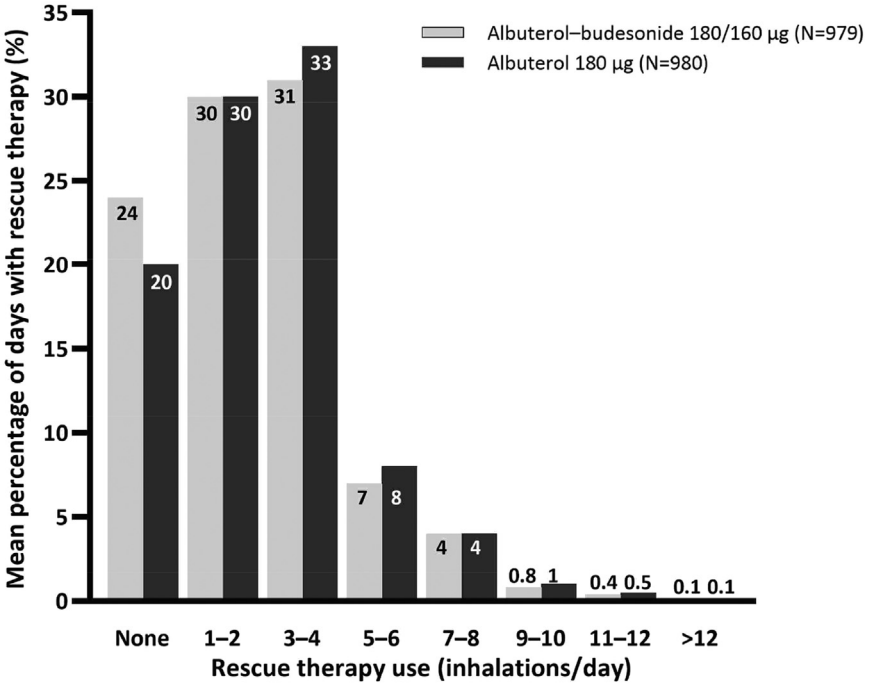


Figure 1. Days with as-needed use of study medication. Full analysis set.

Safety by Inhaled Corticosteroid Maintenance Dose

The mean total durations of treatment for albuterol–budesonide and albuterol groups for each ICS dose category were the following: low-dose ICS category, 191.1 and 182.8 years; medium-dose ICS category, 375.6 and 372.1 years; high-dose ICS category, 268.8 and 256.5 years, respectively. AE frequencies were similar in the albuterol–budesonide and albuterol groups, irrespective of the ICS maintenance dose category (low dose, 45.7% vs 46.2%; medium dose, 46.5% vs 45.5%; high dose, 47.3% vs 49.2%). Frequencies of local and systemic ICS-associated AEs were also low across ICS maintenance dose categories in both treatment groups (Fig 3A, B). The more common AEs across ICS maintenance dose categories (>2.5% of patients) are found in eFigure 2. The frequency of pneumonia was low (<2% of patients) at all ICS maintenance dose levels in both the albuterol–budesonide and albuterol arms: low-dose ICS, 2 patients (0.9%) in the albuterol–budesonide arm and 0 patient in the albuterol arm; medium-dose ICS, 7 patients (1.6%) and 4 patients (0.9%); and high-dose ICS, 6 patients (1.9%) and 2 patients (0.7%), respectively.

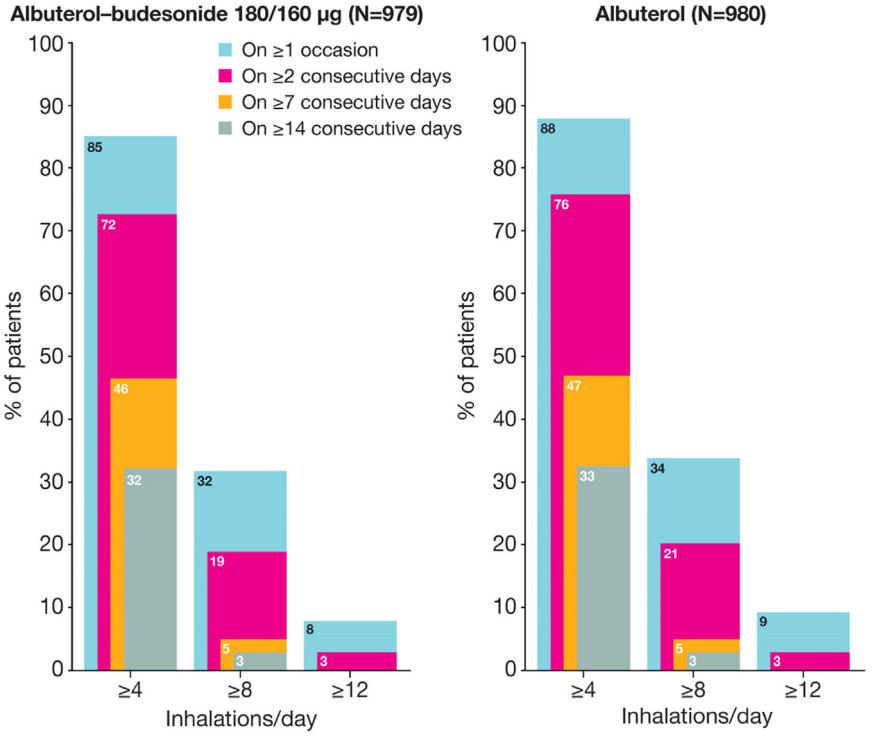


Figure 2. Consecutive days of "high" as-needed use of study medication. Full analysis set.

Table 2
Overview of Adverse Events

Patients with AEs during the treatment period, n (%)	Albuterol–budesonide 180/160 μg (n = 981)	Albuterol 180 μg (n = 981)
Any AE	456 (46.5)	458 (46.7)
Any AE causally related to study treatment	21 (2.1)	16 (1.6)
Any SAE	52 (5.3)	45 (4.6)
Any AE leading to treatment discontinuation	10 (1.0)	9 (0.9)
Any AE with an outcome of death[a]	4 (0.4)	1 (0.1)
More common AEs[b]		
Nasopharyngitis	74 (7.5)	53 (5.4)
Headache	42 (4.3)	48 (4.9)
COVID-19	43 (4.4)	45 (4.6)
Upper respiratory tract infection	26 (2.7)	24 (2.4)
Bronchitis	24 (2.4)	27 (2.8)
Hypertension	22 (2.2)	26 (2.7)
Asthma	18 (1.8)	31 (3.2)
Back pain	26 (2.7)	20 (2.0)
Sinusitis	15 (1.5)	23 (2.3)

Abbreviations: AE, adverse event; SAE, serious adverse event.
NOTE. Safety population; patients aged 18 years or older in the albuterol–budesonide 180/160 μg and albuterol 180 μg groups.
[a]Albuterol–budesonide 180/160 μg: 2 cases of COVID-19, 1 case of blood glucose increased (hyperglycemia/type 2 diabetes mellitus) and 1 cardiac arrest; albuterol 180 μg: 1 case of COVID-19. None were considered treatment related.
[b]Incidence of 2% or more in either treatment group.

Discussion

Patterns of as-needed use were similar in patients receiving albuterol–budesonide or albuterol, indicating that patients used both rescue therapies in a similar manner. This finding also suggests that the addition of ICS to albuterol in the same inhaler does not alter patient behavior regarding rescue use. The similar frequencies in rescue use in the 2 groups may be more reflective of as-needed use in response to symptoms that are the result of variability in inflammation leading to airway narrowing.[12,26] Patients need to use rescue therapy at the first symptoms to prevent future exacerbations. The patient population of the MANDALA study had moderate-to-severe asthma and still experienced symptoms on maintenance therapy. Rescue therapy was used on an as-needed basis, as decided by the patient, up to a maximum of 12 inhalations (6 doses) per day. Under the same conditions, patients using albuterol–budesonide rescue therapy would be expected to experience similar variability of airway inflammation leading to triggering of asthma to those using albuterol monotherapy rescue (as any environmental triggers will be present for both groups) and are not expected to be less likely to use rescue therapy in response to symptoms. Furthermore, patients were instructed to use the study medication before exercise and as they would normally use their albuterol inhaler. Therefore, the similar rates of rescue therapy use in the 2 groups are not an unexpected finding.

Although the mean use of rescue therapy was 2.6 inhalations (1.3-1.4 doses) per day, it is in line with a population of patients with uncontrolled moderate-to-severe persistent asthma as an average across the total study period. Of note, patients in the albuterol–budesonide and albuterol groups used no rescue therapy on 24% and 20% of days, respectively, and patients in both groups used 2 inhalations (1 dose) or less on half of the study days. In addition, high daily use of albuterol–budesonide or albuterol was uncommon, typically short in duration, and was not associated with a meaningful increase in the frequency of AEs. This supports the label-recommended dose of albuterol–budesonide: 180/160 μg (as 2 inhalations) taken as needed for asthma symptoms to a maximum of 6 doses (12 inhalations) per 24 hours.[22]

As-needed albuterol–budesonide 180/160 μg was well tolerated over 24 to 52 weeks in patients with moderate-to-severe asthma, with a safety profile similar to that of albuterol 180 μg, regardless of rescue or maintenance ICS dose. The safety profiles of albuterol and budesonide are well characterized,[27,28] with no new safety findings emerging from their combination in this study. The frequency of AEs was comparable between treatment groups, both overall and with increasing mean as-needed use per day.

The more common AEs in both treatment groups were nasopharyngitis, headache, and COVID-19. Although the proportion of patients with pneumonia was numerically higher in the albuterol–budesonide group than the albuterol group, the numbers of events were low, and it was not possible to draw conclusions. The frequencies of local and systemic ICS-associated AEs were low in both treatment groups, both overall and by maintenance ICS dose, despite patients not being instructed to use spacers or rinse their mouths after rescue therapy use.

These findings are in line with data from the PREPARE trial, which investigated a free combination of ICS (beclomethasone) plus SABA as rescue medication in Black and Latinx adults with moderate-to-severe asthma on ICS-containing maintenance, and reported no new safety considerations.[29] SAE frequency was similar between patients instructed to use their ICS and SABA inhalers in concert and those who used their SABA without as-needed ICS (12.3% vs 12.1%, respectively), nor were there any substantial between-group differences in the types of SAEs experienced. In addition, the safety of as-needed use of ICS-containing rescue therapy (specifically, budesonide–formoterol single maintenance and reliever therapy) in patients with

Table 3
Local and Systemic ICS-Associated AEs[a] Occurring in More Than 1 Patient in Either Arm

Patients with AEs, n (%)	Albuterol–budesonide 180/160 μg (n = 981)	Albuterol 180 μg (n = 981)
Any local ICS-associated AE	19 (1.9)	13 (1.3)
Oral candidiasis	10 (1.0)	4 (0.4)
Dysphonia	3 (0.3)	4 (0.4)
Oropharyngeal candidiasis	3 (0.3)	1 (0.1)
Dysgeusia	1 (0.1)	2 (0.2)
Candida infection	1 (0.1)	0 (0.0)
Aphonia	1 (0.1)	0 (0.0)
Esophageal candidiasis	0 (0.0)	1 (0.1)
Any systemic ICS-associated AE	32 (3.3)	38 (3.9)
Cataract	2 (0.2)	1 (0.1)
Contusion	6 (0.6)	5 (0.5)
Cortisol decreased	0 (0.0)	2 (0.2)
Depression	4 (0.4)	3 (0.3)
Diabetes mellitus[b]	4 (0.4)	5 (0.5)
Diabetic metabolic decompensation	0 (0.0)	2 (0.2)
Hyperglycemia	2 (0.2)	2 (0.2)
Insomnia	4 (0.4)	4 (0.4)
Rib fracture	1 (0.1)	3 (0.3)
Stress fracture	0 (0.0)	2 (0.2)
Type 2 diabetes mellitus	3 (0.3)	1 (0.1)
Wrist fracture	0 (0.0)	2 (0.2)

Abbreviations: AE, adverse event; ICS, inhaled corticosteroid; MedDRA, Medical Dictionary for Regulatory Activities.
NOTE. Safety population; patients aged 18 years or older in the albuterol–budesonide 180/160 μg and albuterol 180 μg groups.
[a]AEs associated with local ICS effects were identified using MedDRA preferred terms, as described in the eMethods.
[b]Type not specified.

Table 4
AEs by Mean Daily As-Needed Use

Patients with AEs n/N (%)	Albuterol–budesonide 180/160 μg (n = 981)	Albuterol 180 μg (n = 981)
>0-<3 inhalations/d	258/592 (43.6)	246/551 (44.6)
≥3-<6 inhalations/d	170/334 (50.9)	182/369 (49.3)
≥6 inhalations/d	28/48 (58.3)	27/52 (51.9)

Abbreviation: AE, adverse event.
NOTE. Safety population.

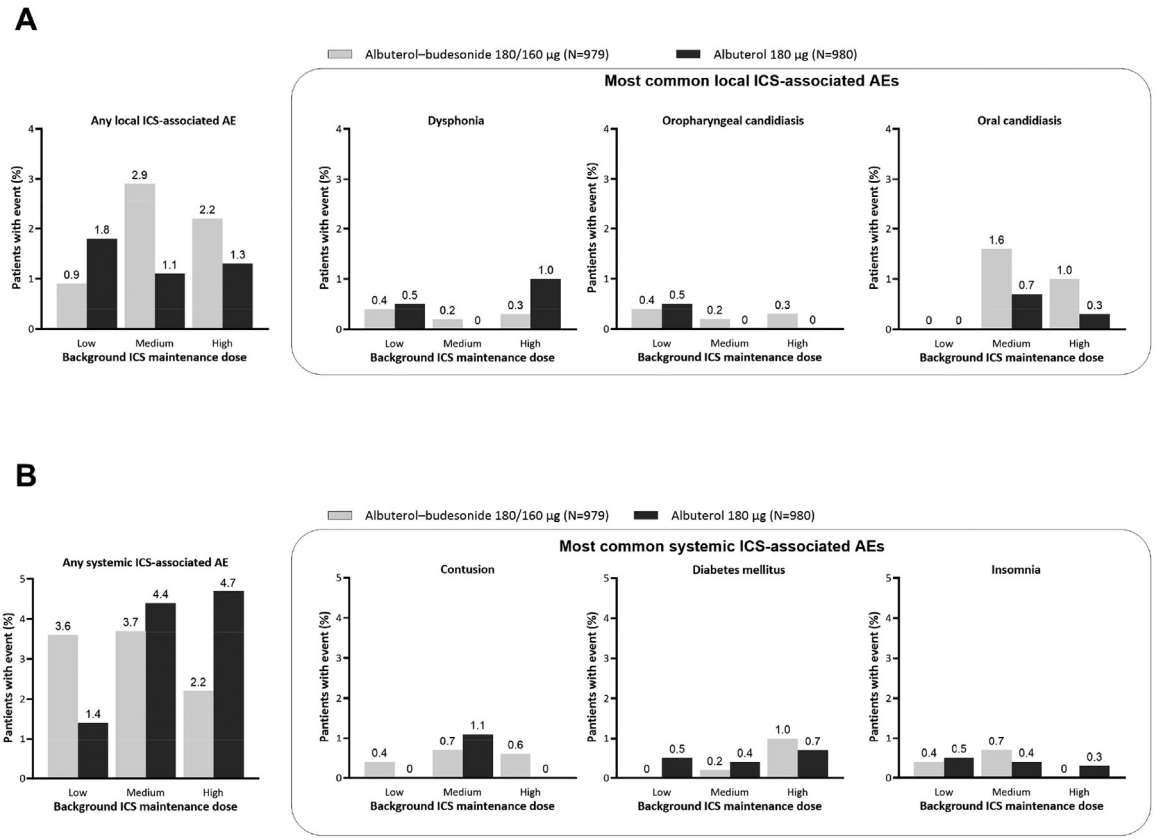


Figure 3. Local (A) and systemic (B) ICS-associated AEs by ICS maintenance dose. [a]Safety analysis set. Information on baseline daily dose of maintenance ICS available for 1950 of the 1962 patients. AE, adverse event; ICS, inhaled corticosteroid.

moderate-to-severe asthma is supported by an extensive evidence base comprising 10 double-blind clinical trials (n = 18,367), more than 16 open-label studies (n = 23,361), and several meta-analyses.[30]

The positive safety profile of albuterol–budesonide supports its use as a rescue therapy, especially as there was no apparent increase in the frequencies of ICS-associated local or systemic AEs. At present, patients often prioritize quick relief of symptoms over the need for daily maintenance therapy and rely heavily on SABA monotherapy inhalers for rescue, which relieve symptoms but not inflammation, with detrimental consequences.[4,9,19,31-33] Real-world findings from a US claims-based study of patients aged 12 years or older receiving SABA monotherapy for rescue found that as annual SABA fills increased, exacerbation risk and SCS prescription claims increased.[34] Cumulative, lifetime SCS exposures as low as a prednisone-equivalent dose of 500 to 1000 mg are associated with increased risk for short- and long-term adverse outcomes including type 2 diabetes mellitus, depression/anxiety, renal impairment, cataracts, cardiovascular disease, pneumonia, and osteoporosis.[35] Based on real-world US claims data (2010-2017) for SABA and ICS maintenance fills from 577,394 patients aged 12 years or older, the total ICS exposure estimated from use of a SABA–ICS rescue therapy on top of ICS-based maintenance therapy did not exceed FDA-approved ICS dosing at each treatment step.[36] Unlike in MANDALA, in which mean adherence to maintenance therapy was more than 75%, real-world patients are typically less adherent to their maintenance regimen, reducing their overall exposure to ICS but increasing their risk of exacerbations.[5,9] Given the reduction in annual exacerbation rates and the resulting reduction in SCS prescriptions, the use of ICS-containing rescue therapies is projected to reduce corticosteroid exposure and associated adverse health outcomes.[5,36]

In general, ICS-containing rescue therapies address the increases in airway inflammation that underlie both exacerbation events and their preceding symptoms and reduce patient reliance on SABA and exposure to SCS.[5,8,30,37] Consequently, the GINA 2024 report includes SABA–ICS, such as albuterol–budesonide, as a rescue option at all therapy steps for patients aged 12 years or older.[4]

Strengths of this analysis include that patients reported being adherent to maintenance therapy, allowing for the evaluation of potential increases in ICS-associated AEs. The data suggest that minimal safety issues result from the addition of ICS to rescue therapy. Limitations include that study medication use was recorded by patients, rather than captured directly by the pMDI device, and that patterns of use and adherence found in clinical trials may not reflect unmonitored real-world use. Patients in this study had a higher bronchodilator responsiveness at the first study visit than expected for this population (approximately 28% forced expiratory volume in 1 second reversibility, compared with the study eligibility criterion of ≥12%). This may indicate a lack of asthma control with their treatment at baseline; for such patients, receiving an ICS as part of their rescue therapy is expected to mitigate the inflammation underlying their high bronchodilator responsiveness and their risk of exacerbations.

In conclusion, this *post hoc* analysis of the MANDALA study revealed that patients' patterns of use of as-needed albuterol–budesonide were similar to those administering as-needed albuterol. These data provide robust evidence of the safety of albuterol–budesonide 180/160 µg when used in addition to maintenance therapies.

Acknowledgments

The authors thank Lucy Cooper, MS, and Amanda Sheldon, PhD, CMPP, of Springer Health+, an International Health division of Springer Nature, for medical writing support.

Disclosures

Dr Chipps is an advisor for, has received consultancy fees from, and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi Genzyme. Dr Panettieri Jr reports receiving grants and advisory board support from AstraZeneca, Sanofi, Genentech, Medimmune, Origa Pharma, Amgen, Research Institute for Fragrance Material, National Institutes of Health, Regeneron, and Novartis. Dr Skolnik served on advisory boards and as consultant for AstraZeneca, Teva, Lilly, Boehringer Ingelheim, Sanofi, Sanofi Pasteur, GlaxoSmithKline, Bayer, Genentech, Abbott, Idorsia, Merck, and Novartis; is a speaker for AstraZeneca, Boehringer Ingelheim, Lilly, GlaxoSmithKline, Bayer, and Heartland; and has received research support from Sanofi, AstraZeneca, GlaxoSmithKline, Bayer, and Novo Nordisk. Dr Cappelletti is a former employee of, and holds stock in, AstraZeneca. Dr Daoud, Ms Dunsire, and Dr Gilbert are employees of, and hold stock in, AstraZeneca. Professor Papi reports receiving grants from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, TEVA, and Sanofi and consulting fees and honoraria for lectures or advisory boards from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi, IQVIA, Avillion, Elpen Pharmaceuticals, Menarini, Zambon, and Mundipharma.

Funding

The MANDALA study was sponsored by Bond Avillion 2 Development LP; statistical analyses reported here were funded by AstraZeneca. Medical writing support was funded by AstraZeneca.

References

1. Centers for Disease Control and Prevention. Most recent national asthma data. Accessed December 7, 2023. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.
2. Engelkes M, de Ridder MAJ, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, et al. Multinational cohort study of mortality in patients with asthma and severe asthma. *Respir Med*. 2020;165:105919.
3. Song HJ, Blake KV, Wilson DL, Winterstein AG, Park H. Health-related quality of life and health utilities of mild, moderate, and severe asthma: evidence from the Medical Expenditure Panel Survey. *J Asthma Allergy*. 2021;14:929–941.
4. Global Initiative for Asthma (GINA). Global Strategy Asthma Management and Prevention 2024. Accessed July 18, 2024. Available at: https://ginasthma.org.
5. Papi A, Chipps BE, Beasley R, Jr Panettieri RA, Israel E, Cooper M, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med*. 2022;386(22):2071–2083.
6. Jackson DJ, Pelaia G, Emmanuel B, Tran TN, Cohen D, Shih VS, et al. Benralizumab in severe eosinophilic asthma by previous biologic use and key clinical subgroups: real-world XALOC-1 programme. *Eur Respir J*. 2024;64(1):2301521.
7. Patrawala S, Ramsey A, Mustafa SS. Steroid stewardship in allergy/immunology: an opportunity for improved clinical outcomes. *Ann Allergy Asthma Immunol*. 2025;134(2):133–134.
8. Thamrin C, Nydegger R, Stern G, Chanez P, Wenzel SE, Watt RA, et al. Associations between fluctuations in lung function and asthma control in two populations with differing asthma severity. *Thorax*. 2011;66(12):1036–1042.
9. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the Inspire study. *BMC Pulm Med*. 2006;6:13.
10. Israel E, Farooqui N, Gillette C, Gilbert I, Gandhi H, Tervonen T, et al. A discrete choice experiment to assess patient preferences for asthma rescue therapy and disease management. *J Allergy Clin Immunol Pract*. 2023;11(9). 2781-2791.e4.
11. Lanz MJ, Gilbert IA, Gandhi HN, Pollack M, Tkacz JP, Lugogo NL. Patterns of rescue and maintenance therapy claims surrounding a clinical encounter for an asthma exacerbation. *Ann Allergy Asthma Immunol*. 2023;131(4). 458-465.e1.
12. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer C-A, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. *Am J Respir Crit Care Med*. 1999;160(2):594–599.
13. Busse W, Stempel D, Aggarwal B, Boucot I, Forth R, Raphiou I, et al. Insights from the AUSTRI study on reliever use before and after asthma exacerbations. *J Allergy Clin Immunol Pract*. 2022;10(7):1916–1918. .e2.
14. Demey L, Van Muylem A, Malinovschi A, Haccuria A, Perez-Bogerd S, Michils A. Exploring the sites and kinetics of bronchodilator response to β-2 agonists in asthma. *J Appl Physiol*. 2021;130(4):1106–1113.
15. Bateman ED, Price DB, Wang H-C, Khattab A, Schonffeldt P, Catanzariti A, et al. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. *Eur Respir J*. 2022;59(5):2101402.
16. Bloom CI, Cabrera C, Arnetorp S, Coulton K, Nan C, van der Valk RJP, et al. Asthma-related health outcomes associated with short-acting β_2-agonist inhaler use: an observational UK study as part of the SABINA global program. *Adv Ther*. 2020;37(10):4190–4208.
17. Lanz MJ, Pollack M, Gilbert IA, Gandhi HN, Tkacz JP, Lugogo NL. Patterns of rescue and maintenance medication claims surrounding an asthma exacerbation in patients treated as intermittent or mild persistent asthma. *J Asthma Allergy*. 2024;17:871–877.
18. Lugogo NL, Gilbert IA, Gandhi HN, Tkacz JP, Lanz MJ. Exacerbation burden in patients treated as intermittent or mild-persistent asthma using short-acting β_2-agonist rescue. *Ann Allergy Asthma Immunol*. 2025;134(5):539–547.e1.
19. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020;55(4):1901872.
20. Quint JK, Arnetorp S, Kocks JWH, Kupczyk M, Nuevo J, Plaza V, et al. Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. *J Allergy Clin Immunol Pract*. 2022;10(9). 2297-2309.e10.
21. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC)Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, et al. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217–1270.
22. Astra Zeneca PLC. Airsupra: prescribing information. Accessed July 27, 2023. Available at: https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/fe598cda-d255-4446-998e-617607f61552/fe598cda-d255-4446-998e-617607f61552_viewable_rendition__v.pdf.
23. Papi A, Chipps BE, Beasley R, Panettieri Reynold A, Israel E, Cooper M, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma: a plain language summary of the MANDALA study. *Ther Adv Respir Dis*. 2024;18:17534666241232264.
24. Global Initiative for Asthma (GINA). Global Strategy Asthma Management and Prevention 2023. Accessed December 7, 2023. Available at: https://ginasthma.org.
25. Global Initiative for Asthma (GINA). Global Strategy Asthma Management and Prevention 2020. Accessed December 8, 2023. Available at: https://ginasthma.org.
26. Frey U, Suki B. Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, and disease progression and control. *Lancet*. 2008;372(9643):1088–1099.
27. Christensson C, Thorén A, Lindberg B. Safety of inhaled budesonide. *Drug Saf*. 2008;31(11):965–988.
28. Marques L, Vale N. Salbutamol in the management of asthma: a review. *Int J Mol Sci*. 2022;23(22):14207.
29. Israel E, Cardet JC, Carroll JK, Fuhlbrigge AL, She L, Rockhold FW, et al. Reliever-triggered inhaled glucocorticoid in Black and Latinx adults with asthma. *N Engl J Med*. 2022;386(16):1505–1518.
30. Cardet JC, Papi A, Reddel HK. "As-needed" inhaled corticosteroids for patients with asthma. *J Allergy Clin Immunol Pract*. 2023;11(3):726–734.
31. Canonica GW, Paggiaro P, Blasi F, Musarra A, Richeldi L, Rossi A, et al. Manifesto on the overuse of SABA in the management of asthma: new approaches and new strategies. *Ther Adv Respir Dis*. 2021;15:17534666211042534.
32. Kaplan A, Mitchell PD, Cave AJ, Gagnon R, Foran V, Ellis AK. Effective asthma management: is it time to let the AIR out of SABA? *J Clin Med*. 2020;9(4):921.
33. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J*. 2017;50(3):1701103.
34. Lugogo N, Gilbert I, Tkacz J, Gandhi H, Goshi N, Lanz MJ. Real-world patterns and implications of short-acting β(2)-agonist use in patients with asthma in the United States. *Ann Allergy Asthma Immunol*. 2021;126. 681-689.e1.
35. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Jie JLZ, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193–204.
36. Lugogo N, Gilbert I, Pollack M, Gandhi H, Tkacz J, Lanz MJ. Estimating inhaled corticosteroid exposure from short-acting β_2-agonist-inhaled corticosteroid rescue. *J Asthma Allergy*. 2023;16:579–584.
37. Lipworth B, Kuo CR, Stewart K, Chan R. Budesonide/formoterol or budesonide/albuterol as anti-inflammatory reliever therapy for asthma. *J Allergy Clin Immunol Pract*. 2024;12(4):889–893.

Supplementary Data

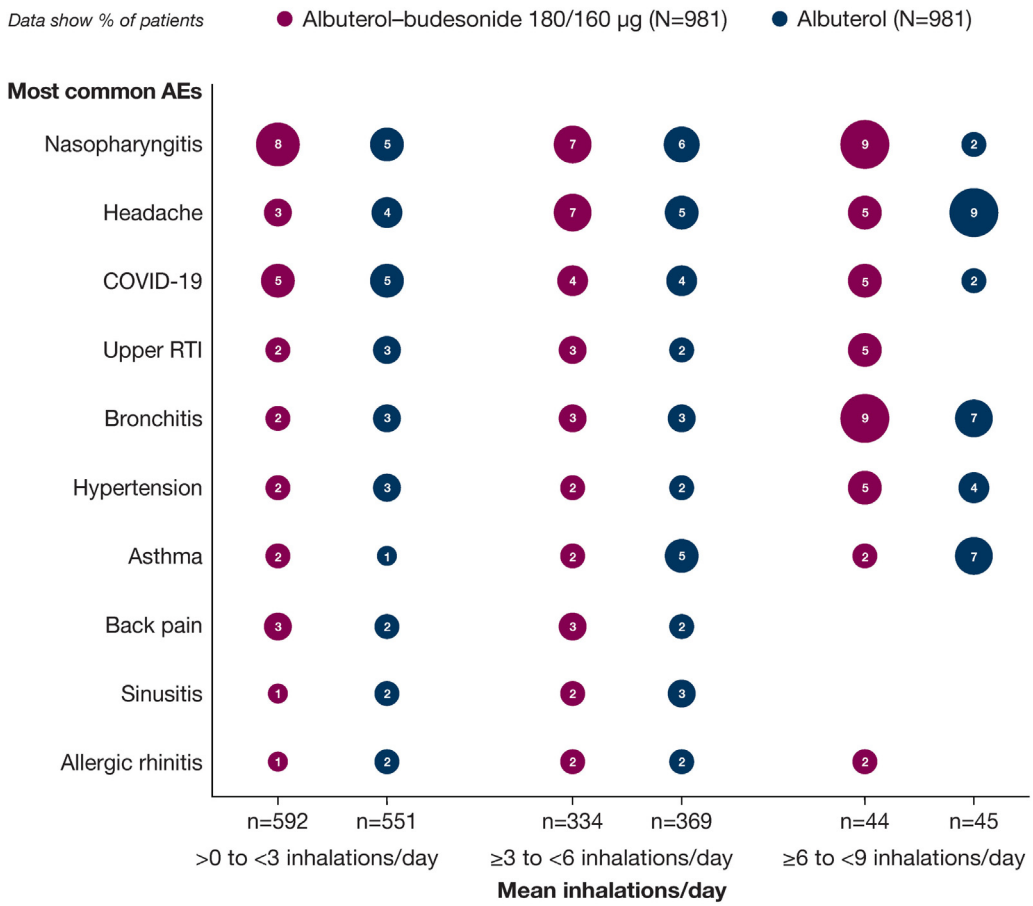
eMethods

Adverse events associated with local inhaled corticosteroid effects were identified using the following MedDRA (Medical Dictionary for Regulatory Activities, version 24.0) preferred terms:

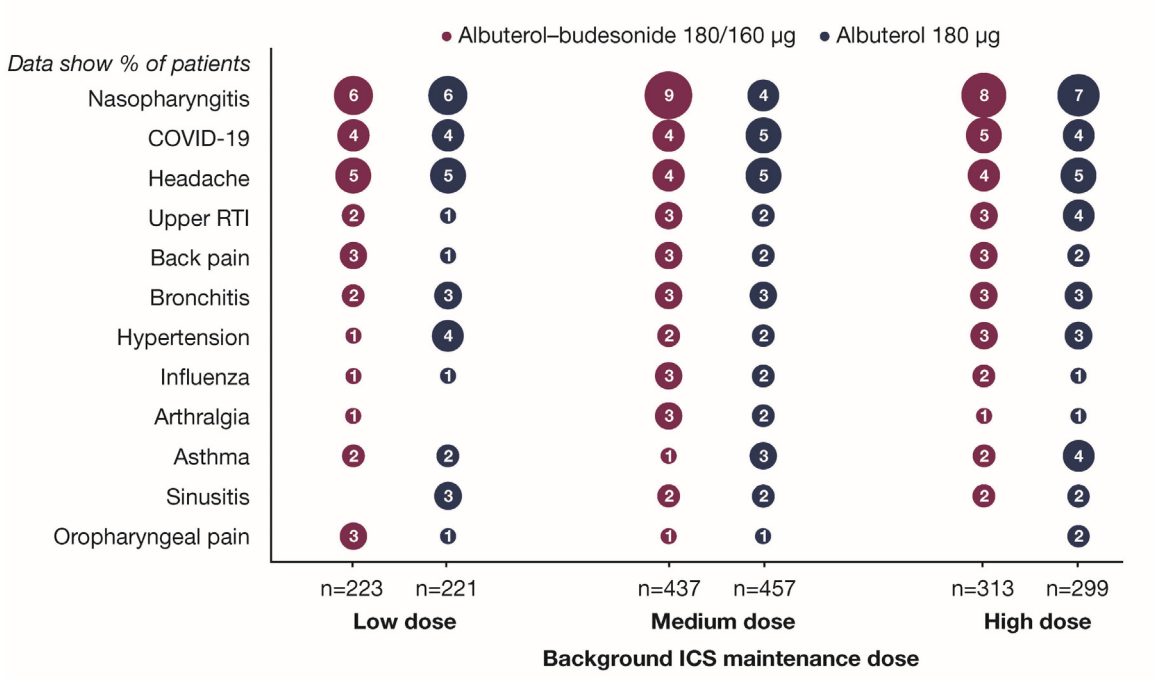
- Oral candidiasis
- Oropharyngeal candidiasis
- Oral fungal infection
- Paradoxical bronchospasm
- Dysphonia

Adverse events associated with systemic inhaled corticosteroid effects were identified using the following preferred terms:

- Hypercorticism
- Adrenal suppression
- Reduction in bone mineral density (including fractures)
- Glaucoma
- Cataracts



eFigure 1. More common adverse events (>2% of patients in at least 1 group) by mean as-needed use of rescue therapy over the treatment period per day. [a]Safety population; patients aged 18 years or older. [b]Data on number of inhalations per day missing for 16 patients. Patients were instructed to use study medication as 2 inhalations of albuterol–budesonide 90/80 µg or albuterol 90 µg. AE, adverse event; RTI, respiratory tract infection.



eFigure 2. More common adverse events (>2.5% of patients in at least 1 group) according to inhaled corticosteroid maintenance dose categories. [a]Safety population; patients aged 18 years or older. [b]Daily dose of maintenance ICS is based on prescribed maintenance medication at baseline and categorized per GINA 2020 guidelines. GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; RTI, respiratory tract infection.

eTable 1
Inhaled Corticosteroid Dose Categories for Patients Aged 12 Years or Older, per Global Initiative for Asthma 2020 Guidelines[24]

ICS	Total daily ICS dose, μg		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle,[a] HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (pMDI, extrafine particle,[a] HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100-250	>250-500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

Abbreviations: DPI, dry powder inhaler; HFA, hydrofluoroalkane propellant; ICS, inhaled corticosteroid; pMDI, pressurized metered dose inhaler.
[a]Based on product information.

eTable 2
Comparison of AEs Overall and in Patients Aged 65 Years or Older

Patients with AEs during treatment period, n (%)	Overall (age ≥ 18 y)		Patients ≥65 y	
	Albuterol–budesonide 180/160 μg (n = 981)	Albuterol 180 μg (n = 981)	Albuterol–budesonide 180/160 μg (n = 192)	Albuterol 180 μg (n = 197)
Any AE	456 (46.5)	458 (46.7)	104 (54.2)	97 (49.2)
Any SAE	52 (5.3)	45 (4.6)	13 (6.8)	10 (5.1)
Most common AEs[a]				
Nasopharyngitis	74 (7.5)	53 (5.4)	17 (8.9)	9 (4.6)
Headache	42 (4.3)	48 (4.9)	11 (5.7)	14 (7.1)
COVID-19	43 (4.4)	45 (4.6)	5 (2.6)	6 (3.0)
Upper respiratory tract infection	26 (2.7)	24 (2.4)	0 (0.0)	0 (0.0)
Back pain	26 (2.7)	20 (2.0)	11 (5.7)	3 (1.5)
Bronchitis	24 (2.4)	27 (2.8)	5 (2.6)	7 (3.6)
Hypertension	22 (2.2)	26 (2.7)	6 (3.1)	5 (2.5)
Asthma	18 (1.8)	31 (3.2)	3 (1.6)	6 (3.0)
Pneumonia	15 (1.5)	6 (0.6)	6 (3.1)	2 (1.0)
Sinusitis	15 (1.5)	23 (2.3)	2 (1.0)	6 (3.0)
Gastroenteritis	11 (1.1)	4 (0.4)	5 (2.6)	2 (1.0)
Rhinitis	11 (1.1)	11 (1.1)	5 (2.6)	3 (1.5)
Cough	9 (0.9)	9 (0.9)	3 (1.6)	5 (2.5)
Anxiety	6 (0.6)	5 (0.5)	4 (2.1)	1 (0.5)

Abbreviations: AE, adverse event; SAE, serious adverse event.
NOTE. Safety population; patients aged 18 years or older in the albuterol–budesonide 180/160 μg and albuterol 180 μg groups.
[a]Most common AEs include those with an incidence more than or equal to 2% in either treatment group and either age group.