The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2022 VOL. 386 NO. 22

Albuterol Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

ABSTRACT

BACKGROUND

As asthma symptoms worsen, patients typically rely on short-acting β_2-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.

METHODS

We conducted a multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapies, which were continued throughout the trial. Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide (with each dose consisting of two actuations of 90 μg and 80 μg, respectively [the higher-dose combination group]), a fixed-dose combination of 180 μg of albuterol and 80 μg of budesonide (with each dose consisting of two actuations of 90 μg and 40 μg, respectively [the lower-dose combination group]), or 180 μg of albuterol (with each dose consisting of two actuations of 90 μg [the albuterol-alone group]). Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group. The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.

RESULTS

A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P=0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P=0.052). The incidence of adverse events was similar in the three trial groups.

CONCLUSIONS

The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. (Funded by Avillion; MANDALA ClinicalTrials.gov number, NCT03769090.)

From the Department of Respiratory Medicine, University of Ferrara Medical School, Ferrara, Italy (A.P.); the Capital Allergy and Respiratory Disease Center, Sacramento, CA (B.E.C.); the Medical Research Institute of New Zealand, Capital and Coast District Health Board, and Victoria University Wellington all in Wellington, New Zealand (R.B.); Rutgers Institute for Translational Medicine and Science, Child Health Institute of New Jersey, Rutgers, the State University of New Jersey, New Brunswick (R.A.P.); Brigham and Women s Hospital, Harvard Medical School, Boston (E.I.); BioPharmaceuticals Research and Development, AstraZeneca, Cambridge (M.C., L.D.), and Avillion, London (A.J.-E., R.R.) both in the United Kingdom; BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden (E.J.); BioPharmaceuticals Research and Development, AstraZeneca, Durham, NC (C.C.); and Avillion, Northbrook, IL (F.C.A.). Dr. Papi can be contacted at ppa@unife.it or at the University of Ferrara Medical School, Via Aldo Moro, 8, 44141, Ferrara, Italy.

Drs. Papi and Chipps contributed equally to this article.

This article was published on May 15, 2022, at NEJM.org.

N Engl J Med 2022;386:2071-83.
DOI: 10.1056/NEJMoa2203163

A Quick Take is available at NEJM.org

Asthma is a heterogeneous disease that manifests as variable airflow obstruction with recurring symptoms driven by underlying persistent, yet fluctuating, airway inflammation.[1] During a loss of asthma control, patients often focus on obtaining immediate symptom relief by relying on their rescue medication, typically a short-acting β_2-agonist (SABA).[2,3] However, SABAs have little effect on underlying airway inflammation,[1,4] and overreliance on SABAs serves as a metric for poor asthma control, with an associated risk of severe asthma exacerbation.[5-10] Because severe asthma exacerbations contribute to considerable morbidity and mortality, the prevention of exacerbations is imperative in the management of asthma.

Concerns regarding adverse consequences associated with overreliance on SABAs and evidence that rescue use of a fixed-dose combination of an inhaled glucocorticoid and formoterol, as compared with a SABA, significantly reduced the risk of exacerbation among patients with a range of asthma severity[11-14] led the Global Initiative for Asthma (GINA)[1,15,16] and the National Asthma Education and Prevention Program[4,17] to generally recommend as-needed use of this combination as the preferred rescue-treatment strategy. Rapid-onset bronchodilators, such as formoterol and albuterol, are ideal for a rescue fixed-dose combination with an inhaled glucocorticoid, as compared with slower-onset bronchodilators, such as salmeterol.[18] However, among patients with moderate-to-severe asthma, data regarding this strategy are limited to the as-needed use of the same agents (budesonide plus formoterol) in the same inhaler device the patients had been using for maintenance therapy.[13,14,19-22] Therefore, evaluation of an inhaled glucocorticoid with a fast-acting bronchodilator in a fixed-dose combination as a rescue medication that could be used in addition to any inhaled glucocorticoid-containing maintenance therapy, as compared with SABA as a rescue medication, is warranted. A fixed-dose combination of inhaled albuterol and budesonide, as compared with albuterol alone, as a rescue medication was considered to be most appropriate, because albuterol is the most commonly used rescue medication worldwide, and SABAs are the only class of rescue medication approved by the Food and Drug Administration in the United States.[4,8,23]

A new formulation of albuterol and budesonide[24,25] in a single pressurized metered-dose inhaler was developed as albuterol inhaled glucocorticoid rescue therapy for the control of acute asthma symptoms, the treatment and prevention of bronchoconstriction, and the prevention of exacerbations. The primary objective of the MANDALA trial was to evaluate the efficacy and safety of as-needed use of albuterol budesonide, as compared with as-needed use of albuterol alone, in patients with moderate-to-severe asthma.

Methods

Patients

Symptomatic patients with asthma who were 4 years of age or older and had had at least one severe asthma exacerbation in the previous 12 months were recruited. Severe asthma exacerbation was defined as clinical deterioration of asthma, with a worsening or a new onset of symptoms leading to at least one of the following events: 3 or more consecutive days of treatment with a systemic glucocorticoid to treat worsening symptoms of asthma (a single depot injection was considered to be equivalent to a 3-day burst); an emergency department or urgent care visit of less than 24 hours during which systemic glucocorticoids were used to treat worsening symptoms of asthma; or an in-patient hospitalization for 24 hours or more because of asthma. Additional inclusion criteria were a forced expiratory volume in 1 second (FEV_1) of 40 to less than 90% of the predicted normal value (with no upper limit for patients 4 to 17 years of age); FEV_1 reversibility of at least 12%, as measured during an in-clinic screening visit; and a score on the Asthma Control Questionnaire 5 (ACQ-5) of 1.5 or greater at visit 2 (day 1 of the double-blind treatment period), which indicates poorly controlled asthma.[26]

The patients had been receiving a medium-to-high dose of inhaled glucocorticoid or a low-to-high dose of inhaled glucocorticoid long-acting β_2-agonist combination, as defined by GINA,[1] with or without another controller, for at least 3 months with stable dosing for at least 4 weeks before screening. They continued to receive their maintenance medications throughout the trial. Major exclusion criteria were chronic obstructive pulmonary disease or other notable lung disease, use of a systemic glucocorticoid within 3 months before screening, and use of

biologic treatments within 3 months or for a duration of 5 half-lives before screening.

TRIAL DESIGN

The MANDALA trial was a multinational, phase 3, double-blind, randomized, parallel-group, event-driven trial with a minimum duration of 24 weeks. The trial was conducted at 295 sites in North America, South America, Europe, and South Africa[27] and was continued until at least 570 first events of severe asthma exacerbation had been reported (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[27]

Adults and adolescents were randomly assigned in a 1:1:1 ratio to one of three treatment groups: a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide (with each dose consisting of two actuations of 90 μg and 80 μg, respectively [the higher-dose combination group]), a fixed-dose combination of 180 μg of albuterol and 80 μg of budesonide (with each dose consisting of two actuations of 90 μg and 40 μg, respectively [the lower-dose combination group]), or 180 μg of albuterol (with each dose consisting of two actuations of 90 μg [the albuterol-alone group]). The trial medications were delivered through a pressurized metered-dose inhaler. Children 4 to 11 years of age were randomly assigned to the lower-dose combination group or to the albuterol-alone group owing to concerns about higher doses of inhaled glucocorticoids in this younger population. The patients were instructed on the proper technique for using the pressurized metered-dose inhaler, and their technique was checked and confirmed by the staff at the trial site. The patients were told to use the trial medications as needed in response to symptoms and that the trial medications could be used before exercise. Rescue use was limited to the trial medications throughout the trial; additional fast-acting bronchodilators, including nebulizers, were prohibited for rescue use. Changes in maintenance therapy were discouraged unless clinically indicated. Details on permitted and prohibited medication use during the trial are provided in the Supplementary Appendix.

The trial procedures have been described previously.[27] Adherence to maintenance therapy and the use of the assigned trial medication were documented by the patients or their parents or guardians with the use of an electronic diary and were monitored by the investigators and staff at the trial site and by the sponsor (Avillion). The maximum daily dose of a trial medication was 12 inhalations (i.e., 6 doses) for all the patients. Patients who had three or more severe asthma exacerbations within a 3-month period or a total of five or more severe asthma exacerbations were assessed for possible discontinuation of the trial medication.

TRIAL OVERSIGHT

The trial design was approved by the appropriate institutional and national regulatory authorities and ethics committees; all the patients or their guardians provided written informed consent (and assent, if appropriate). An independent data and safety monitoring board reviewed unblinded data every 3 months to monitor safety. Avillion coordinated data management and the statistical analyses in conjunction with the responsible contract research organizations (Syneos Health and Phastar, respectively). All the authors contributed to the design of the trial and the interpretation of the data. The first draft of the manuscript was written by a medical writer (funded by AstraZeneca) under the direction of the authors and in accordance with Good Publication Practice guidelines. All the authors provided critical feedback on the first and subsequent drafts of the manuscript and, along with the sponsor, made the decision to submit the manuscript for publication. All the authors had access to the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

END POINTS

The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis. Secondary efficacy end points were the annualized rate of severe asthma exacerbations, total systemic glucocorticoid exposure for asthma during the treatment period, and response at week 24 on the ACQ-5 (validated for persons ≥6 years of age),[28] the Asthma Quality of Life Questionnaire (AQLQ+12, validated for persons ≥12 years of age), and the Pediatric Asthma Quality of Life Questionnaire (PAQLQ, validated for persons aged 7 to 11 years); patients 4 to 6 years of age completed the PAQLQ with the help of a caregiver.[29] Scores on the ACQ-5 range

from 0 to 6, with lower scores indicating better asthma control (minimum clinically important difference, −0.5 points).[30] Scores on both the AQLQ+12 and the PAQLQ range from 1 to 7, with higher scores indicating better asthma-related quality of life (minimum clinically important difference, 0.5 points).[31,32] A response was defined as a decrease (in the ACQ-5 score) or an increase (in the AQLQ+12 or PAQLQ score) of at least 0.5 points from the baseline score.

Safety end points were incident adverse events and incident serious adverse events. These events were assessed from the time that written informed consent (and assent, as appropriate) was obtained through the end of the safety follow-up period (2 weeks after the last in-clinic visit).

STATISTICAL ANALYSIS

The preplanned efficacy analyses were designed to answer the clinical question of interest, that is, whether budesonide, administered in a fixed-dose combination with albuterol on an as-needed basis, provides a benefit that is greater than that with as-needed use of albuterol alone in patients who continued to receive their prescribed maintenance therapy. These analyses used data that were collected during the on-treatment period before treatment discontinuation or a change in maintenance therapy; in the primary end-point analysis, data were censored at the date of treatment discontinuation or a change in maintenance therapy.[27] The results of an alternative, prespecified intention-to-treat analysis that was consistent with the *Journal's* statistical guidelines and included all the data, regardless of a change in maintenance therapy or treatment discontinuation, are presented first in the article. The term preplanned is used when referring to the primary efficacy analysis stated in the statistical analysis plan (with type 1 error control), and the term prespecified is used when referring to the intention-to-treat analysis.

According to the statistical analysis plan (available with the protocol) for the preplanned efficacy analyses, the type I error for the primary end point was controlled for comparisons between each albuterol budesonide dose group and the albuterol-alone group with the use of the Hochberg step-up procedure. Secondary end points were controlled with the use of a hierarchical testing sequence for treatment comparisons between the higher-dose combination group and the albuterol-alone group and between the lower-dose combination group and the albuterol-alone group with respect to each secondary end point. In the alternative intention-to-treat analysis, these type 1 error control procedures were applied in this same manner as in the preplanned efficacy analyses of the primary and secondary end points.

We estimated that a sample of 1000 adults and adolescents per trial group and 570 first events of severe asthma exacerbation would provide the trial with 87% power to detect a 25% lower risk of severe asthma exacerbation with the fixed-dose combination of albuterol budesonide than with albuterol alone, assuming a two-sided significance level of 5% and a probability of a first severe exacerbation event of 0.22 with the use of albuterol alone.[27] In addition, our aim was to recruit 100 children 4 to 11 years of age in accordance with regulatory input.

All patients who had undergone randomization and received any amount of a trial medication, which was classified according to the trial medication they had been assigned to receive, were included in both efficacy analyses comparing the lower-dose combination group with the albuterol-alone group. Children 4 to 11 years of age were not assigned to the higher-dose combination group. Therefore, children 4 to 11 years of age were not included in the albuterol-alone group in the comparison with the higher-dose combination group. The safety analyses included all the patients who had received any amount of a trial medication, which was classified according to the trial medication they had actually received.

The time-to-event analysis of the primary end point of the first severe asthma exacerbation was performed with the use of a Cox proportional-hazards regression model that adjusted for the randomization stratification factors of age group (≥4 to <12, ≥12 to <18, ≥18 to <65, and ≥65 years), geographic region (North America, Western Europe, or South Africa vs. South America and the rest of Europe), and the number of severe asthma exacerbations in the 12 months before screening. The ratio of the hazard rates (hazard ratio) obtained in the primary end-point analysis was used as a measure of the (relative) risk of a severe asthma exacerbation event in order to make it distinct from the annualized rate of severe asthma exacerbations obtained in the secondary analysis.

The annualized rate of severe asthma exacerbations was analyzed with the use of a negative

binomial regression model that adjusted for age, geographic region, number of severe asthma exacerbations in the 12 months before screening, and person-time at risk. Total systemic glucocorticoid exposure per patient was calculated as the annualized total dose of systemic glucocorticoids (in milligrams per year), which was analyzed with the use of a Wilcoxon rank-sum test. The response variables with respect to the ACQ-5, the AQLQ+12, and the PAQLQ at week 24 were compared among the trial groups with the use of a logistic-regression model that adjusted for baseline values, the randomization stratification factors, and the number of severe asthma exacerbations in the 12 months before screening.

RESULTS

PATIENTS

A total of 5620 patients were enrolled in the trial between December 27, 2018, and July 30, 2021. Among these patients, 3132 underwent randomization, 3123 were assessed with respect to the efficacy end points (5 patients who had not received any trial medication and 4 who had been withdrawn because of randomization at more than one site were excluded), and 3127 were assessed with respect to the safety end points (Fig. 1). Data are presented up to August 23, 2021, the time of the primary database lock; a total of 37 children and adolescents remained in the treatment phase of the trial after database lock to complete 24 weeks, and 1 adolescent remained in the 2-week safety follow-up period after database lock.

The characteristics of the patients at screening are provided in Table 1 and Table S1. At baseline, the mean ACQ-5 score was 2.6 across the three trial groups, a result indicating poorly controlled asthma. During the trial, patients reported that the mean (±SD) percentage of days they had taken their maintenance medication was 74.7±25.6% (median, 84.6%). Adherence was similar in the three trial groups (Table S2). Overall, 39 (1.2%) of the patients had a change in maintenance therapy during the trial (see the Supplementary Appendix).

PRIMARY END POINT

Intention-to-Treat Analysis

The intention-to-treat analysis showed that the risk of a severe asthma exacerbation, in a time-to-event analysis, was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P=0.001) (Fig. 2A). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P=0.052). Further inferential testing was not performed, in accordance with the hierarchical testing strategy applied to this alternative, prespecified analysis to control for type I error.

Preplanned On-Treatment Efficacy Analysis

In the preplanned efficacy analysis that included data collected during the on-treatment period before treatment discontinuation or a change in maintenance therapy, the hazard ratio for severe asthma exacerbation in the higher-dose combination group, as compared with the albuterol-alone group, was 0.73 (95% CI, 0.61 to 0.88). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.83 (95% CI, 0.70 to 0.99) (Fig. 2B). The results of the preplanned time-to-event analyses of the first severe asthma exacerbation according to subgroups are provided in Figure S2.

SECONDARY END POINTS

Intention-to-Treat Analysis

The annualized rate of severe asthma exacerbations was 0.43 (95% CI, 0.33 to 0.58) in the higher-dose combination group and 0.58 (95% CI, 0.44 to 0.77) in the albuterol-alone group (rate ratio, 0.75; 95% CI, 0.61 to 0.91) (Table 2). The annualized rate of severe asthma exacerbations was 0.48 (95% CI, 0.37 to 0.63) in the lower-dose combination group and 0.60 (95% CI, 0.46 to 0.79) in the albuterol-alone group (rate ratio, 0.81; 95% CI, 0.66 to 0.98).

The mean (±SD) annualized total dose of systemic glucocorticoid (in prednisone equivalents) was 83.6±247.7 mg in the higher-dose combination group and 130.0±630.3 mg in the albuterol-alone group. The mean annualized total dose of systemic glucocorticoid was 94.7±318.2 mg in the lower-dose combination group and 127.6±619.8 mg in the albuterol-alone group. Post hoc results of the intention-to-treat analyses of response on the ACQ-5 and the AQLQ+12 are provided in Table 2.

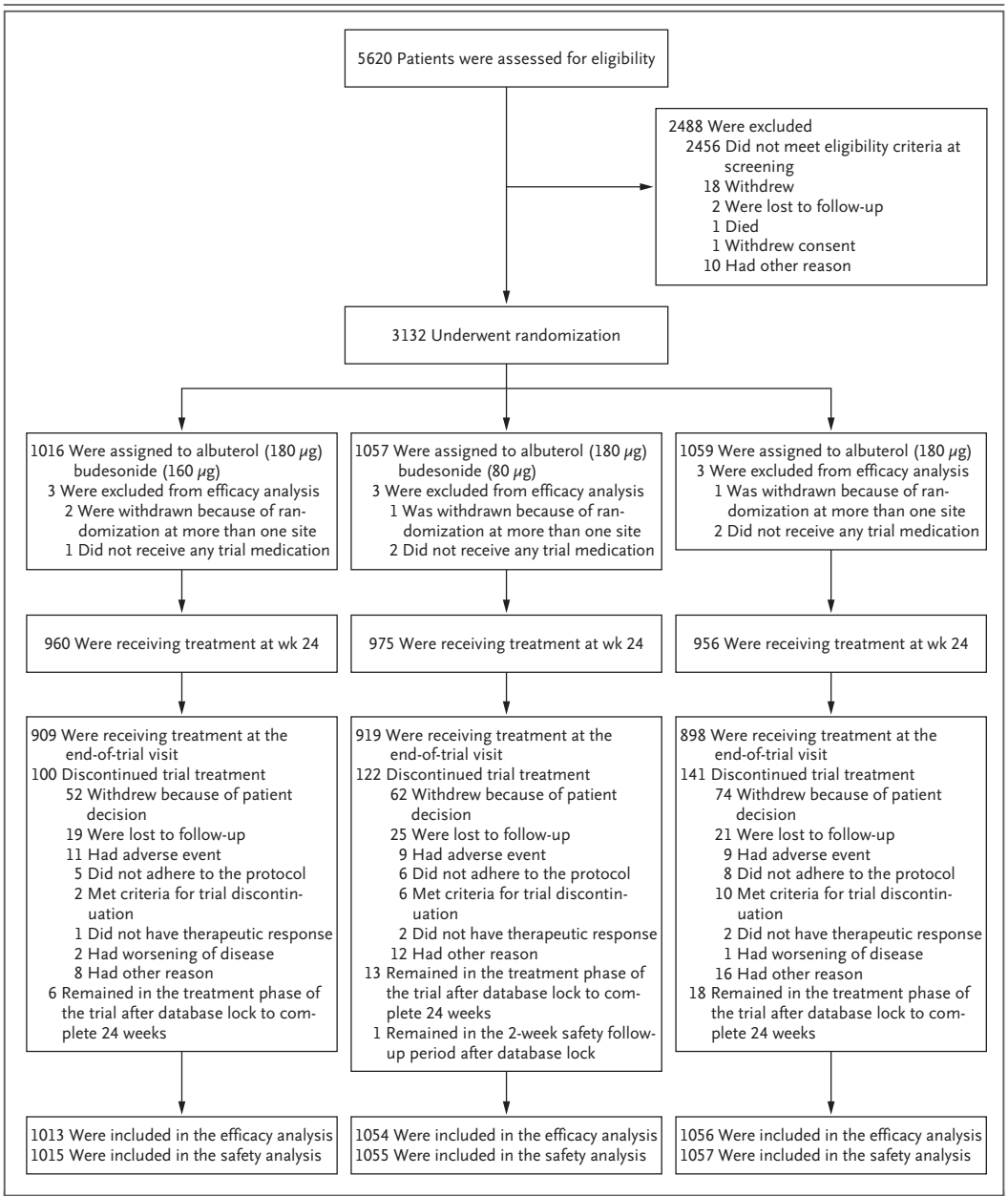


Figure 1. Screening, Randomization, and Analyses.

All 37 patients who remained in the treatment phase of the trial after the primary database lock to complete 24 weeks across the three trial groups were children or adolescents; the 1 patient in the lower-dose combination group who remained in the 2-week safety follow-up period after the primary database lock was an adolescent.

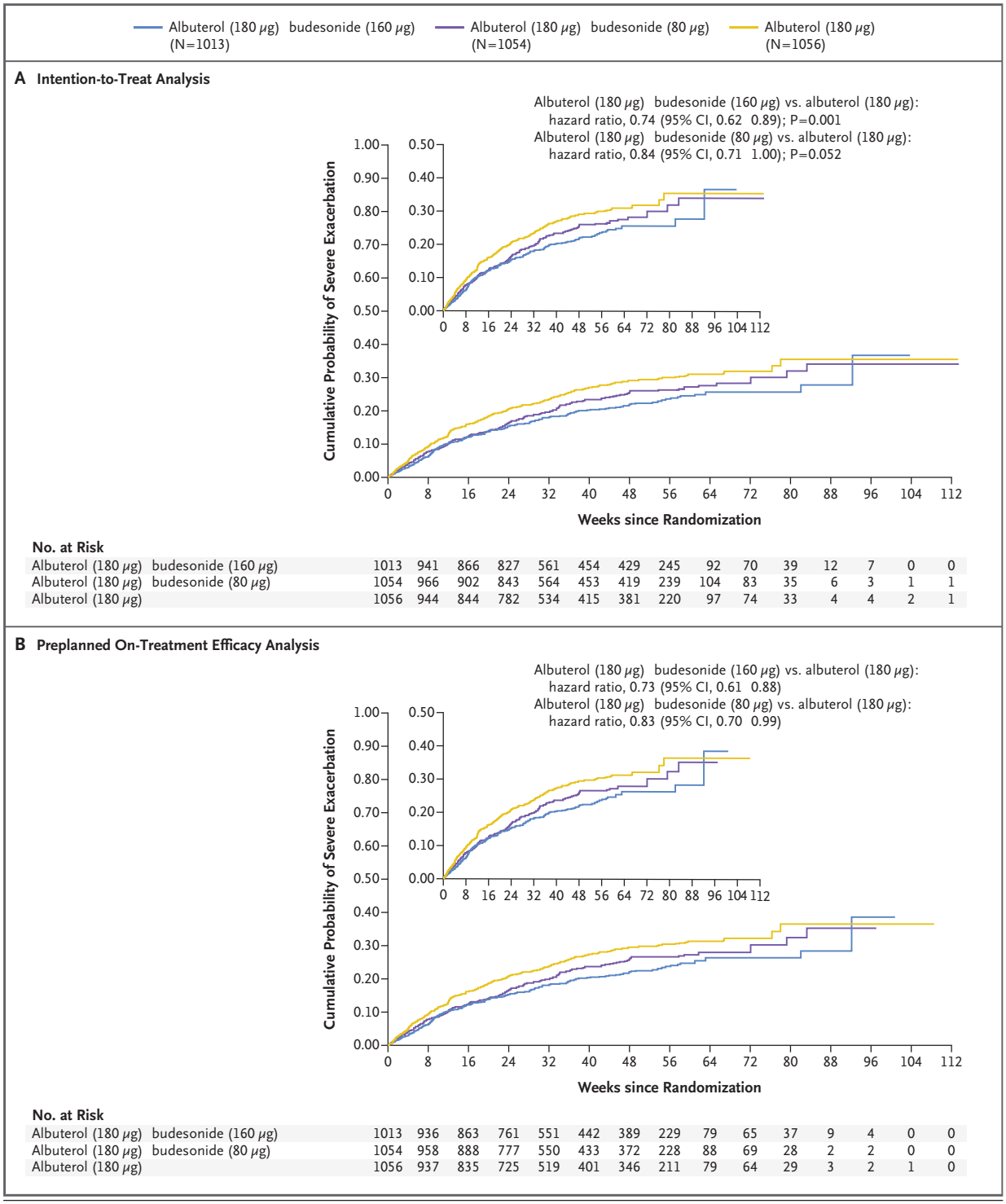
Preplanned On-Treatment Efficacy Analysis

The annualized rate of severe asthma exacerbations was 0.45 (95% CI, 0.34 to 0.60) in the higher-dose combination group and 0.59 (95% CI, 0.44 to 0.78) in the albuterol-alone group (rate ratio, 0.76; 95% CI, 0.62 to 0.93). The annualized rate of severe asthma exacerbations was 0.49 (95% CI, 0.37 to 0.64) in the lower-dose combination group and 0.61 (95% CI, 0.46 to 0.80) in the albuterol-alone group (rate ratio, 0.80; 95% CI,

Table 1. Demographic and Clinical Characteristics of the Patients at Screening.*

Characteristic	Albuterol (180 μg) Budesonide (160 μg) (N=1013)	Albuterol (180 μg) Budesonide (80 μg) (N=1054)	Albuterol (180 μg) (N=1056)	All Patients (N=3123)
Age				
Mean yr	50.6±15.1	48.5±16.7	49.1±17.2	49.4±16.4
Distribution no. (%)				
≥4 to <12 yr	0	41 (3.9)	42 (4.0)	83 (2.7)
≥12 to <18 yr	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
≥18 to <65 yr	787 (77.7)	804 (76.3)	783 (74.1)	2374 (76.0)
≥65 yr	192 (19.0)	177 (16.8)	197 (18.7)	566 (18.1)
Female sex no. (%)	645 (63.7)	685 (65.0)	694 (65.7)	2024 (64.8)
Race or ethnic group no. (%)				
White	818 (80.8)	847 (80.4)	868 (82.2)	2533 (81.1)
Black	139 (13.7)	141 (13.4)	137 (13.0)	417 (13.4)
Asian	29 (2.9)	33 (3.1)	23 (2.2)	85 (2.7)
American Indian or Alaska Native	1 (0.1)	1 (0.1)	0	2 (0.1)
Other	26 (2.6)	32 (3.0)	28 (2.7)	86 (2.8)
Hispanic or Latinx no. (%)				
Yes	233 (23.0)	260 (24.7)	315 (29.8)	808 (25.9)
No	780 (77.0)	794 (75.3)	741 (70.2)	2315 (74.1)
Geographic region no. (%)				
North America, Western Europe, and South Africa	536 (52.9)	556 (52.8)	563 (53.3)	1655 (53.0)
South America and rest of Europe	477 (47.1)	498 (47.2)	493 (46.7)	1468 (47.0)
Prebronchodilator FEV_1				
Mean volume liters	1.9±0.6	1.9 ±0.6	1.9±0.6	1.9±0.6
Mean percent of predicted value	63.4±12.8	64.0±13.7	64.4±13.3	63.9±13.3
Mean reversibility in FEV_1 %	27.7±17.2	27.2±14.2	27.8±15.9	27.6±15.8
Maintenance treatment no. (%)				
Low-dose inhaled glucocorticoid LABA or medium-dose inhaled glucocorticoid	314 (31.0)	334 (31.7)	308 (29.2)	956 (30.6)
Medium-dose inhaled glucocorticoid LABA or high-dose inhaled glucocorticoid	385 (38.0)	435 (41.3)	441 (41.8)	1261 (40.4)
High-dose inhaled glucocorticoid LABA	295 (29.1)	267 (25.3)	285 (27.0)	847 (27.1)
Missing	19 (1.9)	18 (1.7)	22 (2.1)	59 (1.9)
Severe asthma exacerbations in the 12 mo before screening no. (%)				
1	788 (77.8)	822 (78.0)	840 (79.5)	2450 (78.5)
2	185 (18.3)	185 (17.6)	164 (15.5)	534 (17.1)
3	27 (2.7)	38 (3.6)	45 (4.3)	110 (3.5)
≥4	13 (1.3)	9 (0.9)	7 (0.7)	29 (0.9)

* Plus minus values are means ±SD. The analysis includes 3123 patients; 5 patients who had not received any amount of a trial medication and 4 who had been withdrawn because of randomization at more than one site were excluded. Medications for rescue use were limited to the trial medications throughout the trial; additional fast-acting bronchodilators, including nebulizers, were prohibited. Additional controller medications were used by approximately 15% of the patients: approximately 10% used a leukotriene-receptor antagonist, 4% a long-acting muscarinic antagonist, and 2% a xanthine. Changes to maintenance therapy were allowed when clinically indicated (see the Supplementary Appendix). FEV_1 denotes forced expiratory volume in 1 second, and LABA long-acting β_2-agonist.
The results were obtained from the visit in which the prebronchodilator FEV_1 was assessed for eligibility.
The results were obtained from the visit in which reversibility in FEV_1 was assessed for eligibility. The reversibility in FEV_1 was calculated as the postbronchodilator FEV_1 (in liters) minus the prebronchodilator FEV_1 (in liters) divided by the prebronchodilator FEV_1 (in liters).



0.66 to 0.98) (Table 2). The number of patients with at least one severe asthma exacerbation that led to hospitalization was 9 in the higher-dose combination group, 10 in the lower-dose combination group, and 17 in the albuterol-alone group (Table S3). The number of patients with at least one severe asthma exacerbation that led to emergency department or urgent care visits was 49 in

Figure 2 (facing page). Time-to-Event Analysis of the First Event of Severe Asthma Exacerbation (Primary End Point).

Data are presented for all the patients. Children 4 to 11 years of age were excluded in the comparison between the higher-dose combination group and the albuterol-alone group; therefore, the number of patients in the albuterol-alone group in this comparison (1014 patients) was lower than that in the comparison with the lower-dose combination group, in which children 4 to 11 years of age were included. The anticipated probability of a first event of severe asthma exacerbation among the patients who received albuterol alone was 0.22.

the higher-dose combination group, 50 in the lower-dose combination group, and 66 in the albuterol-alone group.

The mean annualized total dose of systemic glucocorticoid (in prednisone equivalents) was 86.2±262.9 mg in the higher-dose combination group and 129.3±657.2 mg in the albuterol-alone group (Table 2). The mean annualized total dose of systemic glucocorticoid was 95.5±335.4 mg in the lower-dose combination group and 127.1± 646.2 mg in the albuterol-alone group.

At week 24, a response on the ACQ-5 (i.e., a decrease of at least 0.5 points from the baseline score) was observed in 66.8% of the patients in the higher-dose combination group and in 62.1% of those in the albuterol-alone group, for an odds ratio of 1.22 (95% CI, 1.02 to 1.47). A response on the ACQ-5 was observed in 64.7% of the patients in the lower-dose combination group and in 61.6% of those in the albuterol-alone group, for an odds ratio of 1.13 (95% CI, 0.95 to 1.35). A response on the AQLQ+12 at week 24 (i.e., an increase of at least 0.5 points from the baseline score) was observed in 51.1% of the patients in the higher-dose combination group, in 49.5% of those in the lower-dose combination group, and in 46.4% of those in the albuterol-alone group, for an odds ratio of 1.23 (95% CI, 1.02 to 1.48) in the comparison between the higher-dose combination group and the albuterol-alone group and an odds ratio of 1.11 (95% CI, 0.93 to 1.34) in the comparison between the lower-dose combination group and the albuterol-alone group. The results of the ACQ-5, AQLQ+12, and PAQLQ response analyses are provided in Table 2 and Table S4. The results with respect to the preplanned exploratory end points of prebronchodilator FEV_1, morning and evening peak expiratory flow, and daytime and night-time symptoms of asthma are summarized in the Supplementary Appendix.

TRIAL MEDICATION USE

The overall pattern of as-needed use of trial medications was similar in the three trial groups, with increased use around the time of clinical deterioration of asthma (Fig. S3). Patients reported using 2 or fewer inhalations on the majority of trial days (mean percentage of days with ≤2 inhalations: 53.7% in the higher-dose combination group, 52.6% in the lower-dose combination group, and 51.0% in the albuterol-alone group), and patients reported using more than 8 inhalations on less than 2% of trial days (Fig. S4). Average daily as-needed use was similar in the three trial groups, with a mean of 2.6 inhalations per day in the higher-dose combination group, 2.7 inhalations per day in the lower-dose combination group, and 2.8 inhalations per day in the albuterol-alone group, which is equal to approximately 1.3, 1.3, and 1.4 doses, respectively, of trial medication per day.

SAFETY END POINTS

The percentage of patients with any adverse event was similar in the three trial groups: 46.2% in the higher-dose combination group, 47.1% in the lower-dose combination group, and 46.4% in the albuterol-alone group (Table S5). The percentage of patients with serious adverse events, including deaths, was 5.2% in the higher-dose combination group, 3.8% in the lower-dose combination group, and 4.5% in the albuterol-alone group. The percentage of patients with adverse events leading to discontinuation of the trial medication was 1.0% in the higher-dose combination group, 0.9% in the lower-dose combination group, and 0.9% in the albuterol-alone group. Seven patients had died four in the higher-dose combination group (two from coronavirus disease 2019 [Covid-19], one from an elevated glucose level, and one from cardiac arrest), two in the lower-dose combination group (one from Covid-19 and one from lung metastasis with pneumothorax), and one in the albuterol-alone group (from Covid-19). No deaths were considered by the trial investigators to be related to the trial medication.

The most common adverse events were nasopharyngitis, headache, and upper respiratory

Table 2. Intention-to-Treat and Preplanned On-Treatment Efficacy Analyses of the Secondary End Points.*

Analysis	Intention-to-Treat Analysis				Preplanned On-Treatment Efficacy Analysis			
	Adults and Adolescents		Adults, Adolescents, and Children		Adults and Adolescents		Adults, Adolescents, and Children	
	Albuterol (180 μg) Budesonide (160 μg)	Albuterol (180 μg)	Albuterol (180 μg) Budesonide (80 μg)	Albuterol (180 μg) Alone	Albuterol (180 μg) Budesonide (160 μg)	Albuterol (180 μg)	Albuterol (180 μg) Budesonide (80 μg)	Albuterol (180 μg)
Annualized rate of severe asthma exacerbation								
Patients no.	1013	1014	1054	1056	1013	1014	1054	1056
Severe exacerbations no.	345	427	372	441	334	413	354	426
Annualized rate (95% CI)	0.43 (0.33 0.58)	0.58 (0.44 0.77)	0.48 (0.37 0.63)	0.60 (0.46 0.79)	0.45 (0.34 0.60)	0.59 (0.44 0.78)	0.49 (0.37 0.64)	0.61 (0.46 0.80)
Rate ratio (95% CI)	0.75 (0.61 0.91)	Reference	0.81 (0.66 0.98)	Reference	0.76 (0.62 0.93)	Reference	0.80 (0.66 0.98)	Reference
Annualized total dose of systemic glucocorticoid								
Patients no.	1012	1011	1052	1052	1012	1011	1052	1052
Median value (5th 95th percentile) mg/yr	0.0 (0.0 459.2)	0.0 (0.0 484.3)	0.0 (0.0 494.4)	0.0 (0.0 600.8)	0.0 (0.0 496.1)	0.0 (0.0 622.1)	0.0 (0.0 487.0)	0.0 (0.0 615.9)
Mean value mg/yr	83.6±247.7	130.0±630.3	94.7±318.2	127.6±619.8	86.2±262.9	129.3±657.2	95.5±335.4	127.1±646.2
Response analysis at wk 24								
ACQ-5								
Patients no.	1013	1014	1052	1055	1013	1014	1052	1055
Patients with response no. (%)	682 (67.3)	636 (62.7)	690 (65.6)	656 (62.2)	677 (66.8)	630 (62.1)	681 (64.7)	650 (61.6)
Odds ratio (95% CI)	1.22 (1.01 1.46)	Reference	1.15 (0.96 1.37)	Reference	1.22 (1.02 1.47)	Reference	1.13 (0.95 1.35)	Reference
AQLQ+12								
Patients no.	994	993	987	NA	994	993	987	NA
Patients with response no. (%)	515 (51.8)	464 (46.7)	496 (50.3)	NA	508 (51.1)	461 (46.4)	489 (49.5)	NA
Odds ratio (95% CI)	1.25 (1.04 1.50)	Reference	1.13 (0.94 1.36)	NA	1.23 (1.02 1.48)	Reference	1.11 (0.93 1.34)	NA

* Plus minus values are means ±SD. The hierarchical testing procedure was stopped after the comparison between the lower-dose combination group and the albuterol-alone group in the intention-to-treat analysis of the primary end point; therefore, 95% confidence intervals cannot be used to infer treatment effects. A total of 3123 patients were assessed with respect to the efficacy end points (5 patients who had not received any trial medication and 4 who had been withdrawn because of randomization at more than one site were excluded). The comparisons between the higher-dose combination group and the albuterol-alone group excluded children 4 to 11 years of age; therefore, the number of patients in the albuterol-alone group in these comparisons was less than that in the comparisons between the lower-dose combination group and the albuterol-alone group. NA denotes not applicable.
Analyses included patients 12 years of age or older.
Analyses included patients 4 years of age or older, except for the Asthma Control Questionnaire 5 (ACQ-5) response analysis, in which patients 4 and 5 years of age were excluded, and the Asthma Quality of Life Questionnaire (AQLQ+12) response analysis, in which patients 4 to 11 years of age were excluded.
The annualized total dose of systemic glucocorticoid is given in prednisone equivalents.
Intention-to-treat analyses for the ACQ-5 response and the AQLQ+12 response are post hoc. Scores on the ACQ-5 range from 0 to 6, with lower scores indicating better asthma control (minimum clinically important difference, 0.5 points). Scores on the AQLQ+12 range from 1 to 7, with higher scores indicating better asthma-related quality of life (minimum clinically important difference, 0.5 points). A response was defined as a decrease (in the ACQ-5 score) or an increase (in the AQLQ+12 score) of at least 0.5 points from the baseline score.

tract infections; Covid-19 was recorded in 4.2 to 4.9% of patients (Table 3). The percentage of patients with adverse events associated with the use of inhaled glucocorticoids was similar in the three trial groups, ranging from 1.3% in the albuterol-alone group to 2.0% in the higher-dose combination group (Table S6). The three most common adverse events associated with the use of inhaled glucocorticoids were oral candidiasis (1.0% in the higher-dose combination group, 0.9% in the lower-dose combination group, and 0.5% in the albuterol-alone group), dysphonia (0.4%, 0.6%, and 0.4%, respectively), and oropharyngeal candidiasis (0.3%, 0.3%, and 0.1%, respectively).

DISCUSSION

Among patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapy, the risk of severe asthma exacerbation was significantly lower with a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide, administered on an as-needed basis in two actuations of 90 μg and 80 μg, respectively, than with as-needed albuterol alone. The results were similar in the intention-to-treat analysis and in the analysis that included data collected during the on-treatment period before treatment discontinuation or a change in maintenance therapy. The findings in both analyses showed that the annualized rate of severe asthma exacerbations was numerically lower with each albuterol budesonide dose than with albuterol and that the mean total systemic glucocorticoid exposure among the patients in the higher-dose combination group was numerically lower than that in the albuterol-alone group. Both doses of albuterol budesonide had an acceptable safety profile that was consistent with that of the active components, with no safety concerns identified.

The pattern of rescue use of the trial medications was similar in the three trial groups, as assessed on the basis of the percentage of trial days with rescue use and use around the time of clinical deterioration of asthma, which was increased in all three groups. The finding of a mean number of medication doses per day of less than 1.5 across the three trial groups shows that the patients used the albuterol budesonide combination as they used albuterol alone. Unlike albuterol monotherapy, the fixed-dose combination allows patients to adjust the dose of inhaled glucocorticoid according to their own symptom-driven use of a bronchodilator in response to worsening asthma episodes.

The findings from the MANDALA trial with respect to a reduction in the risk of exacerbations are consistent with those from previous trials of the inclusion of an inhaled glucocorticoid when rescue medication is taken, as shown in a trial of as-needed use of albuterol beclomethasone as compared with as-needed use of albuterol alone in patients with mild asthma[33] and in a more recent real-world, open-label trial of a free combination of beclomethasone in addition to a rescue medication in Black patients and Latinx patients with uncontrolled moderate-to-severe asthma.[34] Similarly, multiple trials that evaluated the single maintenance and reliever therapy (SMART) strategy, in which the same agents (budesonide plus formoterol) used as maintenance therapy are used as rescue therapy, as compared with rescue therapy with a SABA in addition to budesonide plus formoterol as maintenance therapy, showed a reduction in the risk of exacerbation in patients with moderate-to-severe asthma.[12,22,35] The use of albuterol budesonide as rescue medication in the current trial addresses the limited data regarding the rescue use of inhaled glucocorticoid formoterol, for which data are lacking in patients receiving maintenance treatment with an alternative inhaled glucocorticoid long-acting β_2-agonist combination or inhaled glucocorticoid alone. Given the risks and limitations of SABA alone as rescue therapy, national and international recommendations call for an inhaled glucocorticoid-containing rescue medication as the preferred as-needed treatment; the data from this trial support that approach. Given its acceptable safety profile, the greater efficacy of the fixed-dose combination than of albuterol alone, as well as the absence of a need to change underlying maintenance therapy, indicates that this fixed-dose combination could replace SABA alone as rescue therapy in patients with moderate-to-severe asthma.

The strengths of our trial are the low dropout rate, with 93% of the patients completing at least 24 weeks of the treatment period, despite the trial having been conducted during the global Covid-19 pandemic, and the multinational and double-blind trial design, which increased external and internal validity, respectively. Albuterol

Table 3. Adverse Events Occurring in at Least 2% of Patients in Any Trial Group.*

Event	Albuterol (180 μg) Budesonide (160 μg) (N=1015)	Albuterol (180 μg) Budesonide (80 μg) (N=1055)	Albuterol (180 μg) (N=1057)
	number of patients (percent)		
Any adverse event	469 (46.2)	497 (47.1)	490 (46.4)
Nasopharyngitis	76 (7.5)	61 (5.8)	54 (5.1)
Headache	44 (4.3)	50 (4.7)	50 (4.7)
Covid-19	43 (4.2)	52 (4.9)	46 (4.4)
Upper respiratory tract infection	26 (2.6)	31 (2.9)	26 (2.5)
Bronchitis	25 (2.5)	27 (2.6)	28 (2.6)
Hypertension	22 (2.2)	27 (2.6)	26 (2.5)
Asthma	18 (1.8)	20 (1.9)	35 (3.3)
Back pain	27 (2.7)	23 (2.2)	20 (1.9)
Influenza	21 (2.1)	23 (2.2)	14 (1.3)
Sinusitis	15 (1.5)	17 (1.6)	24 (2.3)

* Adverse events are sorted in decreasing total frequency of preferred term in the *Medical Dictionary for Regulatory Activities*, version 24.0. Patients with multiple events in the same category are counted only once in that category.

budesonide was used in addition to the usual maintenance therapy the patients were receiving, which included a range of inhaled glucocorticoid-containing medications, with the aim of reflecting a real-world population and improving the generalizability of our results. The limitations of our trial are the lack of measurements of the fraction of exhaled nitric oxide level, which would have allowed for a direct assessment of antiinflammatory effects; the small number of children, which precludes conclusions being drawn in this important subpopulation; and the fact that growth indexes could not be assessed because of the small numbers and short period of observation of children in this trial.

In the current phase 3 trial involving patients with uncontrolled moderate-to-severe asthma, the risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide than with as-needed use of albuterol alone.

Supported by Avillion.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial patients and their families; the investigators and staff at the trial sites; the team at Syneos Health and Phastar; the members of the independent data and safety monitoring committee; the full clinical team at Avillion and AstraZeneca; and Marco E. Favretto and Samantha Blakemore at inScience Communications, Springer Healthcare, United Kingdom, for providing medical writing support (funded by AstraZeneca).

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