ORIGINAL ARTICLE

As-Needed Albuterol–Budesonide in Mild Asthma

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ABSTRACT

BACKGROUND

As-needed use of albuterol–budesonide has been shown to result in a significantly lower risk of severe asthma exacerbation than as-needed use of albuterol alone among patients with moderate-to-severe asthma. Data on albuterol–budesonide in mild asthma are needed.

METHODS

We conducted a fully virtual, decentralized, phase 3b, multicenter, double-blind, event-driven trial involving persons 12 years of age or older with disease that was uncontrolled despite treatment for mild asthma with a short-acting β_2-agonist (SABA) with or without a low-dose inhaled glucocorticoid or leukotriene-receptor antagonist. Participants were randomly assigned in a 1:1 ratio to a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide (with each dose consisting of two inhaler actuations of 90 μg and 80 μg, respectively) or 180 μg of albuterol (with each dose consisting of two inhaler actuations of 90 μg) on an as-needed basis for up to 52 weeks. The primary end point was the first severe asthma exacerbation, assessed in a time-to-event analysis, in the on-treatment efficacy population, and the key secondary end point was the first severe exacerbation in the intention-to-treat population. Secondary end points included the annualized rate of severe asthma exacerbations and exposure to systemic glucocorticoids.

RESULTS

A total of 2516 participants underwent randomization; 1797 (71.4%) completed the trial. Of 2421 participants in the full analysis population (1209 assigned to the albuterol–budesonide group and 1212 to the albuterol group), 97.2% were 18 years of age or older; 74.4% used a SABA alone at baseline. The trial was stopped for efficacy at a prespecified interim analysis. A severe exacerbation occurred in 5.1% of the participants in the albuterol–budesonide group and in 9.1% of those in the albuterol group in the on-treatment efficacy population (hazard ratio, 0.53; 95% confidence interval [CI], 0.39 to 0.73) and in 5.3% and 9.4%, respectively, in the intention-to-treat population (hazard ratio, 0.54; 95% CI, 0.40 to 0.73) (P<0.001 for both comparisons). The annualized rate of severe asthma exacerbations was lower with albuterol–budesonide than with albuterol (0.15 vs. 0.32; rate ratio, 0.47; 95% CI, 0.34 to 0.64), as was the mean annualized total dose of systemic glucocorticoids (23.2 vs. 61.9 mg per year). Adverse events were similar in the two treatment groups.

CONCLUSIONS

As-needed use of albuterol–budesonide resulted in a lower risk of a severe asthma exacerbation than as-needed use of albuterol alone among participants with disease that was uncontrolled despite treatment for mild asthma. (Funded by Bond Avillion 2 Development and AstraZeneca; BATURA ClinicalTrials.gov number, NCT05505734.)

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*A complete list of investigators in the BATURA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Mild asthma, which affects between 50% and 70% of patients with a diagnosis of asthma,[1] is often assumed to be low risk.[2] However, severe or fatal exacerbations still occur in persons with infrequent asthma symptoms, with up to 30% of exacerbations and deaths reported in patients treated for mild asthma or who have infrequent symptoms.[3,4]

During periods of asthma worsening, patients often rely on their short-acting β_2-agonist (SABA) rescue therapy alone, which does not address airway inflammation, thus increasing the risk of severe or fatal exacerbations.[3-5] The risk of severe or fatal exacerbations even among persons with infrequent asthma symptoms, a lack of evidence for the efficacy and safety of SABA-only treatment, and the superiority of inhaled glucocorticoid–containing rescue regimens as compared with a SABA alone for improving outcomes led the Global Initiative for Asthma (GINA) to cease recommending the use of a SABA alone in mild asthma.[2] The GINA recommends an inhaled glucocorticoid plus a fast-acting bronchodilator as rescue therapy across all treatment steps for patients 12 years of age or older. Although the fixed-dose combination of an inhaled glucocorticoid and formoterol is approved by the Food and Drug Administration for maintenance therapy, it is not approved for use as rescue therapy.

A retrospective claims study suggested that a "window of opportunity" may exist to prevent a severe exacerbation in patients who have uncontrolled disease despite treatment for mild asthma (defined by the filling of a prescription for a SABA, a maintenance medication appropriate for mild persistent asthma, or both) if symptoms and inflammation are addressed concomitantly.[6] In line with this concept and recommendations from the GINA, the combination of albuterol and budesonide in a single pressurized metered-dose inhaler allows patients to receive an inhaled glucocorticoid when they need it by using their rescue therapy in response to symptoms.[7,8] A pressurized metered-dose inhaler that provides a fixed dose of 180 μg of albuterol and 160 μg of budesonide (with each dose consisting of two actuations of 90 μg and 80 μg, respectively) is FDA-approved for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations among patients 18 years of age or older with asthma.[9] In the MANDALA trial, as-needed use of a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide resulted in a 26% lower risk of a severe asthma exacerbation than as-needed use of 180 μg of albuterol among patients with moderate-to-severe asthma receiving inhaled glucocorticoid–containing maintenance therapy.[7-9]

The objective of the fully home-based, decentralized BATURA trial was to examine the efficacy and safety of as-needed use of a fixed-dose combination of 180 μg of albuterol and 160 μg of budesonide, as compared with as-needed use of 180 μg of albuterol, in participants 12 years of age or older being treated with medications recommended for mild asthma but with uncontrolled disease. In the trial, we investigated the benefit of adding budesonide to albuterol to reduce the risk of a severe asthma exacerbation.[10]

METHODS

TRIAL DESIGN

The design of the BATURA trial was published previously.[10] In brief, the BATURA trial was a U.S.-based, phase 3b, multicenter, randomized, double-blind, parallel-group, event-driven, decentralized superiority trial comparing as-needed use of 180 μg of albuterol and 160 μg of budesonide with as-needed use of 180 μg of albuterol for a minimum of 12 weeks and a maximum of 52 weeks. The trial was completely virtual, with no in-clinic assessments (see the Methods section in the Supplementary Appendix, available with the full text of the article at NEJM.org). All visits were conducted remotely with the use of the telehealth platform Science 37; the visit schedule was reported previously (Fig. S1 in the Supplementary Appendix).[10]

PARTICIPANTS

Participants were recruited with the use of a multichannel approach, with an emphasis on multimedia, multiplatform outreach, including social media, and artificial intelligence technology to identify high-probability, eligibility-matched participants. Eligible participants were those 12 years of age or older who had uncontrolled asthma while taking National Asthma Education and Prevention Program Step 1 or Step 2 treatment, defined as either as-needed SABA only or as-needed SABA plus maintenance low-dose inhaled glucocorticoid or leukotriene-receptor antagonist. The asthma diagnosis was provided by a prescrib-

ing health care professional, with documentation (e.g., medical records or a letter from the treating physician) confirmed by the investigator. Participants were required to have filled at least two prescriptions for a SABA inhaler, or at least one prescription for a SABA inhaler plus at least one prescription for a glucocorticoid inhaler or a leukotriene-receptor antagonist, in the 12 months before enrollment and to have used a SABA for asthma symptom relief on at least 2 days in the 2 weeks before randomization. Other key inclusion criteria were an Asthma Impairment and Risk Questionnaire (AIRQ) score of 2 or higher at screening (on a scale from 0 to 10, with 0 or 1 indicating well controlled, 2 to 4 not well controlled, and 5 to 10 very poorly controlled; further details are provided in the Methods section of the Supplementary Appendix) and access to a smartphone and Internet connection.[10]

TREATMENTS

Participants were randomly assigned in a 1:1 ratio to use albuterol–budesonide or albuterol as needed for 12 to 52 weeks, with stratification according to pretrial asthma medication (SABA only vs. SABA plus low-dose inhaled glucocorticoid or leukotriene-receptor antagonist) and number of previous severe exacerbations (0 vs. ≥1) in the 12 months before screening. Participants continued their own maintenance treatment, if applicable. Trial medications were administered by means of a pressurized metered-dose inhaler as 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) or 180 μg of albuterol (with each dose consisting of two actuations of 90 μg). Participants were instructed to take no more than 12 inhalations (i.e., 6 doses) in a 24-hour period.

TRIAL OVERSIGHT

Participants, or their parent or legal guardian if the participant was younger than 18 years of age, provided electronic informed consent. An independent, external data and safety monitoring committee reviewed unblinded safety data. A trial sponsor (Bond Avillion 2 Development) coordinated data management and the statistical analyses in conjunction with the responsible contract research organizations (Parexel 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 Bond Avillion 2 Development, 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 end point was the first severe asthma exacerbation, assessed in a time-to-event analysis, in the on-treatment efficacy population. The key secondary end point was the first severe asthma exacerbation, assessed in a time-to-event analysis, in the intention-to-treat population. A severe exacerbation was defined as a worsening of symptoms resulting in at least 3 days' use of a systemic glucocorticoid, an emergency department or urgent care visit for asthma warranting systemic glucocorticoids, hospitalization due to asthma, or death, with documentation (e.g., prescription of a systemic glucocorticoid for asthma or hospital evidence reporting treatment for an asthma exacerbation) confirmed by the investigator.[10]

Other secondary end points were the annualized rate of severe asthma exacerbations and annualized total exposure to systemic glucocorticoids, evaluated in the on-treatment efficacy population. Exploratory end points that were evaluated in the on-treatment efficacy population included use of health care resources, the score on the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire, and the AIRQ score (which was also evaluated in the intention-to-treat population). Safety end points were the frequency and types of adverse events and serious adverse events.

STATISTICAL ANALYSIS

Two efficacy analysis populations were defined: the on-treatment efficacy population, for which the analysis included data that were collected during the on-treatment period before the discontinuation of randomized treatment or a step-up in maintenance therapy, and the intention-to-treat population, for which the analysis included all data regardless of these events. The populations

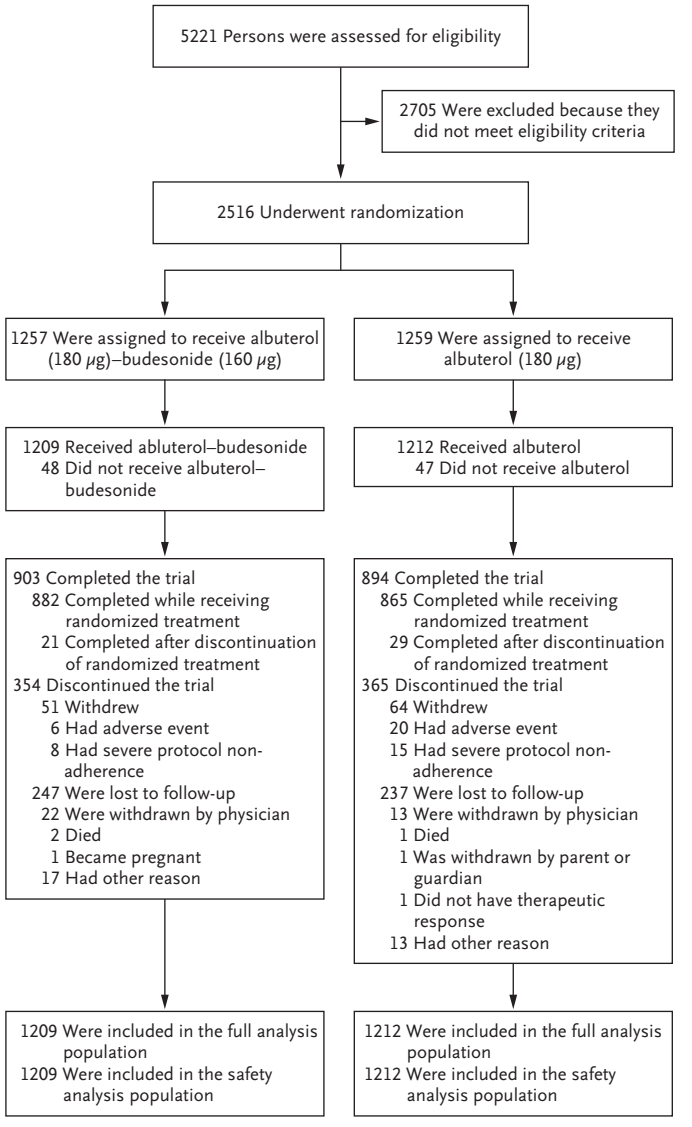

Figure 1. Screening, Randomization, and Follow-up.

were derived from the full analysis population, which included all the participants who underwent randomization and received at least one actuation of trial treatment. Primary and secondary end points were evaluated in the overall population 12 years of age or older and in participants 18 years of age or older. The type I error was controlled across primary and secondary end points with the use of a hierarchical testing procedure (first severe exacerbation in the on-treatment efficacy population, first severe exacerbation in the intention-to-treat population, annualized rate of severe exacerbations, and annualized total exposure to systemic glucocorticoids). Exploratory end points were not included in the hierarchical testing strategy.

Safety end points were evaluated in the safety analysis population, which included all the participants who underwent randomization and received at least one actuation of trial treatment, with data analyzed according to the actual treatment received. Details of the sample-size calculations and analysis models have been published previously[10] (see the Methods section in the Supplementary Appendix).

RESULTS

PARTICIPANTS

A total of 5221 participants from 54 U.S. sites were screened between September 2, 2022, and August 22, 2024, with 2516 undergoing randomization and 2421 included in the full analysis population and the safety analysis population (Fig. 1). A total of 1797 participants (71.4%) completed the trial: 903 in the albuterol–budesonide group and 894 in the albuterol group. The most common reason for withdrawal from this fully virtual trial was loss to follow-up, followed by participant decision. A total of 6 participants in the albuterol–budesonide group and 20 in the albuterol group discontinued the trial because of adverse events.

The demographic and clinical characteristics of the participants at baseline were generally similar in the two treatment groups. The majority of participants (97.2%) were 18 years of age or older, and 74.4% were receiving a SABA alone before the trial. Leukotriene-receptor antagonist and low-dose inhaled glucocorticoid maintenance medications that were used by participants are reported in Table S1. In the 12 months before trial entry, most participants (88.8%) had no severe exacerbations (Table 1 and Table S2). The percentages of participants who reported severe exacerbations resulting in emergency department treatment or hospitalization in the 12 months before trial entry were low (<5% and <1%, respectively) (Table 1). The baseline AIRQ score was similar in the two groups and indicated that participants' asthma was not well controlled (mean [±SD] AIRQ score, 4.8±2.0). Baseline characteristics were similar among participants regardless of trial completion status (Table S3).

The representativeness of the trial population is shown in Table S4.

PRIMARY AND KEY SECONDARY EFFICACY END POINTS

The prespecified interim analysis for the primary and key secondary end points was conducted in June 2024 after 172 severe exacerbation events had been recorded. A hierarchical testing strategy was applied to control the type I error. The decision to stop the trial early was recommended by the data and safety monitoring committee owing to a significantly lower risk of a severe exacerbation with albuterol–budesonide than with albuterol. This effect was observed in both the on-treatment efficacy population (primary end point: percentage with a severe exacerbation, 5.1% vs. 9.1%; hazard ratio, 0.53; 95% confidence interval [CI], 0.39 to 0.73; P<0.001) (Fig. 2A) and the intention-to-treat population (key secondary end point: 5.3% vs. 9.4%; hazard ratio, 0.54; 95% CI, 0.40 to 0.73; P<0.001 (Fig. 2B). Among participants 18 years of age of age or older, treatment with albuterol–budesonide resulted in a lower risk of a severe asthma exacerbation than treatment with albuterol in both the on-treatment efficacy population (6.0% vs. 10.7%; hazard ratio, 0.54; 95% CI, 0.40 to 0.72; P<0.001) and the intention-to-treat population (6.2% vs. 11.2%; hazard ratio, 0.54; 95% CI, 0.41 to 0.72; P<0.001) (Table S5 and Fig. S2). The proportional-hazards assumption was met for all analyses. Missing data were assumed to be censored at random (i.e., the reasons for censoring were unrelated to the risk of having an event). The findings of a sensitivity analysis performed under increasingly conservative informative censoring assumptions was supportive of the findings of the primary analysis (see the tipping-point analysis in the Supplementary Appendix).

OTHER SECONDARY EFFICACY END POINTS

Treatment with albuterol–budesonide resulted in a lower annualized rate of severe asthma exacerbations than treatment with albuterol among participants 12 years of age or older (0.15 vs. 0.32; rate ratio, 0.47; 95% CI, 0.34 to 0.64) and among those 18 years of age or older (0.15 vs. 0.33; rate ratio, 0.46; 95% CI, 0.33 to 0.63) in the on-treatment efficacy population (Table 2). The mean annualized total exposure to systemic glucocorticoids during the treatment period was also lower with albuterol–budesonide than with albuterol in participants 12 years of age or older (23.2 vs. 61.9 mg per year; relative difference, −62.5%) and in those 18 years of age or older (23.0 vs. 63.0 mg per year; relative difference, −63.5%) in the on-treatment efficacy population (Table 2).

EXPLORATORY END POINTS

Average daily use of as-needed trial medication was similar in the two groups, with a mean of 1.5±1.7 inhalations per day in the albuterol–budesonide group and 1.8±2.0 inhalations per day in the albuterol group (on-treatment efficacy population). The mean percentage of days with more than 12 inhalations per day was low: 0.59±3.44% in the albuterol-budesonide group and 1.02±4.36% in the albuterol group. Changes in maintenance medication are shown in Table S6; maintenance therapy was stepped up in 1.8% of the participants in the albuterol–budesonide group and in 2.4% of those in the albuterol group.

The AIRQ score appeared to decrease, indicating improvement, in both treatment groups (Table S7). At week 16, the least-squares mean (±SE) change in the AIRQ score from baseline was −2.95±0.08 with albuterol–budesonide and −2.74±0.08 with albuterol (difference, −0.22; 95% CI, −0.38 to −0.05). By week 52, the least-squares mean changes were −3.35±0.11 and −3.20±0.11, respectively (difference, −0.16; 95% CI, −0.38 to 0.07). There were no apparent differences in EQ-5D-5L scores between groups (Table S8). Measures of health care resource use are summarized in Table S9.

SAFETY

The overall incidence of adverse events was similar in the albuterol–budesonide and albuterol groups (42.2% and 43.5%, respectively) (Table 3). The most common adverse events in both treatment groups were upper respiratory tract infection, coronavirus disease 2019, and nasopharyngitis. Inhaled glucocorticoid–associated local adverse events occurred in less than 2% of the participants in each group: 1.6% in the albuterol–budesonide group and 0.6% in the albuterol group (Table S10). Among participants receiving albuterol–budesonide, the incidence of inhaled glucocorticoid–associated local adverse events appeared to be higher in the subgroup receiving a SABA alone at baseline than in the subgroup receiving a SABA plus a low-dose inhaled gluco-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Full Analysis Population).*

Characteristic	Albuterol–Budesonide (N=1209)	Albuterol (N=1212)	Total Population (N=2421)
Age			
Mean — yr	42.5±14.3	42.9±14.7	42.7±14.5
Distribution — no. (%)			
12 to <18 yr	29 (2.4)	39 (3.2)	68 (2.8)
18 to <65 yr	1100 (91.0)	1073 (88.5)	2173 (89.8)
≥65 yr	80 (6.6)	100 (8.3)	180 (7.4)
Female sex — no. (%)	810 (67.0)	843 (69.6)	1653 (68.3)
Race or ethnic group — no./total no. (%)†			
White	848/1209 (70.1)	849/1211 (70.1)	1697/2420 (70.1)
Black	219/1209 (18.1)	219/1211 (18.1)	438/2420 (18.1)
Asian	28/1209 (2.3)	28/1211 (2.3)	56/2420 (2.3)
Other‡	58/1209 (4.8)	59/1211 (4.9)	117/2420 (4.8)
Multiple	19/1209 (1.6)	24/1211 (2.0)	43/2420 (1.8)
Not reported	37/1209 (3.1)	32/1211 (2.6)	69/2420 (2.9)
Hispanic or Latino ethnic group — no. (%)†	156/1208 (12.9)	136/1211 (11.2)	292/2419 (12.1)
Time since diagnosis of asthma — yr§			
Median (interquartile range)	24.3 (12.4–36.0)	24.1 (12.5–35.3)	24.2 (12.5–35.7)
Range	<0.05–69.7	<0.05–77.8	<0.05–77.8
Time since last severe exacerbation — days¶			
Median (interquartile range)	138 (85–242)	153 (96–250)	146 (91–245)
Range	8–384	29–407	8–407
Associated conditions, triggers, or allergies — no. (%)			
Seasonal conjunctivitis	410 (33.9)	411 (33.9)	821 (33.9)
Atopic dermatitis or eczema	216 (17.9)	224 (18.5)	440 (18.2)
Allergens as asthma trigger	925 (76.5)	962 (79.4)	1887 (77.9)
Aspirin as asthma trigger	24 (2.0)	32 (2.6)	56 (2.3)
Exercise as asthma trigger	935 (77.3)	949 (78.3)	1884 (77.8)
Other asthma trigger	642 (53.1)	666 (55.0)	1308 (54.0)
Nasal polyps	56 (4.6)	59 (4.9)	115 (4.8)
Eczema	203 (16.8)	203 (16.7)	406 (16.8)
Chronic sinusitis	187 (15.5)	183 (15.1)	370 (15.3)
History of sinus surgery	62 (5.1)	84 (6.9)	146 (6.0)
History of positive allergy tests	516 (42.7)	546 (45.0)	1062 (43.9)
Mean AIRQ score‖	4.7±2.0	4.8±2.0	4.8±2.0
Pretrial asthma medication — no. (%)			
SABA only	900 (74.4)	901 (74.3)	1801 (74.4)
SABA plus low-dose inhaled glucocorticoid or LTRA	309 (25.6)	311 (25.7)	620 (25.6)

Table 1. (Continued.)

Characteristic	Albuterol–Budesonide (N=1209)	Albuterol (N=1212)	Total Population (N=2421)
Asthma characteristics during the 12 mo before trial entry			
No. of severe exacerbations — no. of participants (%)			
0	1072 (88.7)	1079 (89.0)	2151 (88.8)
1	127 (10.5)	115 (9.5)	242 (10.0)
2	8 (0.7)	17 (1.4)	25 (1.0)
>2	2 (0.2)	1 (0.1)	3 (0.1)
No. of severe exacerbations resulting in ED treatment — no. of participants (%)			
0	1166 (96.4)	1178 (97.2)	2344 (96.8)
1	42 (3.5)	29 (2.4)	71 (2.9)
2	1 (0.1)	5 (0.4)	6 (0.2)
No. of severe exacerbations resulting in hospitalization — no. of participants (%)			
0	1204 (99.6)	1207 (99.6)	2411 (99.6)
1	5 (0.4)	5 (0.4)	10 (0.4)

* Plus–minus values are means ±SD. The full analysis population included all the participants who underwent randomization and received at least one actuation of trial treatment. Percentages may not total 100 because of rounding. ED denotes emergency department, LTRA leukotriene-receptor antagonist, and SABA short-acting β_2-agonist.
† Race or ethnic group was reported by the participant.
‡ Included are American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and "other."
§ Data were available for 1207 participants in the albuterol–budesonide group and for 1211 participants in the albuterol group.
¶ A severe exacerbation was defined as a worsening of symptoms resulting in at least 3 days' use of systemic glucocorticoids, an ED or urgent care visit for asthma warranting systemic glucocorticoids, hospitalization due to asthma, or death. Data were available for 135 participants in the albuterol–budesonide group and for 132 participants in the albuterol group.
‖ The Asthma Impairment and Risk Questionnaire (AIRQ) is a validated tool comprising 10 yes-or-no questions that assesses both symptom control during the previous 2 weeks and exacerbation risk considering the previous 12 months. A score of 0 or 1 indicates well-controlled asthma; a score of 2, 3, or 4 indicates not well-controlled asthma; and a score of 5 to 10 indicates very poorly controlled asthma.

corticoid or leukotriene-receptor antagonist (1.9% vs. 0.6%).

The percentages of participants reporting serious adverse events were low and similar in the two treatment groups. The only serious adverse event reported in 0.3% or more of the participants in either group was asthma. No serious adverse event was considered by the investigator to be related to a trial drug. The percentages of participants reporting adverse events leading to discontinuation of a trial drug were low in both treatment groups; the only adverse event leading to discontinuation of a trial drug in 0.5% or more of the participants during the randomized treatment period was cough.

Two deaths occurred during the randomized treatment period (Table 3). Neither was judged by the investigator to be related to the trial drug or reported as related to asthma.

DISCUSSION

The BATURA trial showed that as-needed albuterol–budesonide was efficacious in reducing the risk of severe asthma exacerbations among participants 12 years of age or older with uncontrolled

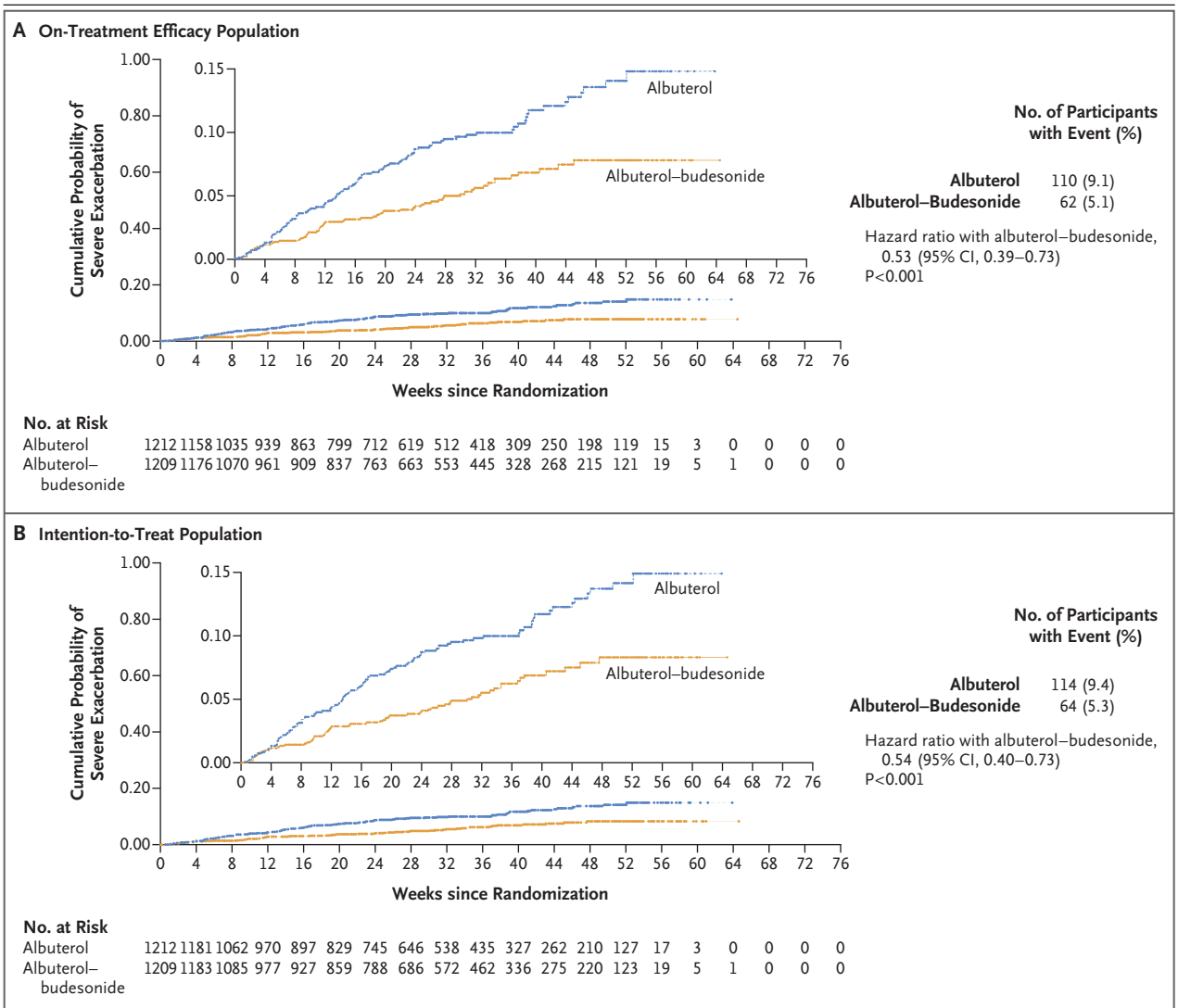

Figure 2. First Severe Asthma Exacerbation.

Panel A shows the first severe asthma exacerbation, assessed in a time-to-event analysis, in the on-treatment efficacy population (primary end point), and Panel B shows the first severe asthma exacerbation, assessed in a time-to-event analysis, in the intention-to-treat population (key secondary end point). The insets show the same data on an expanded y axis. For the on-treatment efficacy population, the analysis included data that were collected during the on-treatment period before the discontinuation of randomized treatment or a step-up in maintenance therapy; for the intention-to-treat population, the analysis included all data regardless of these events. Data are from a prespecified interim analysis that was conducted after 172 severe exacerbation events had been recorded. Hazard ratios and 95% confidence intervals were calculated with the use of a Cox proportional-hazards regression model that was adjusted for treatment, pretrial asthma therapy (short-acting β_2-agonist [SABA] only, low-dose inhaled glucocorticoid plus SABA, or leukotriene-receptor antagonist plus SABA), and the number of severe exacerbations (0 or ≥1) in the 12 months before screening.

disease despite treatment for mild asthma, although it should be noted that more than 97% of the participants were 18 years of age or older. The risk of a severe exacerbation was 47% lower with albuterol–budesonide than with albuterol, which led to the trial being stopped after a planned interim analysis showed efficacy. In addition, at the final data analysis, the annualized rate of severe exacerbations was 53% lower with albuterol–budesonide than with albuterol, and total annualized exposure to systemic glucocorticoids was 63% lower with albuterol–budesonide.

Safety findings showed that the two treatment groups had similar safety profiles. However, the

Table 2. Annualized Rate of Severe Asthma Exacerbations and Annualized Total Exposure to Systemic Glucocorticoids.*

Variable	Full Analysis Population, ≥12 Yr of Age		Full Analysis Population, ≥18 Yr of Age	
	Albuterol–Budesonide (N=1209)	Albuterol (N=1212)	Albuterol–Budesonide (N=1180)	Albuterol (N=1173)
Annualized rate of severe exacerbations				
No. of participants evaluated	1209	1212	1180	1173
No. of first severe exacerbations	83	160	82	159
Time at risk — participant-yr	845.8	823.8	825.7	797.4
Estimated annualized rate (95% CI)	0.15 (0.11 to 0.20)	0.32 (0.25 to 0.41)	0.15 (0.12 to 0.20)	0.33 (0.26 to 0.43)
Rate ratio (95% CI)	0.47 (0.34 to 0.64)	—	0.46 (0.33 to 0.63)	—
P value	<0.001	—	<0.001	—
Annualized total exposure to systemic glucocorticoids†				
No. of participants evaluated	1204	1203	1175	1164
Mean total amount per participant of exposure to systemic glucocorticoids — mg/yr	23.2±142.9	61.9±662.1	23.0±142.4	63.0±672.3
Difference in arithmetic means — mg/yr	−38.7	—	−40.0	—
Percent difference in arithmetic means	−62.5	—	−63.5	—
P value‡	<0.001	—	<0.001	—

* Plus–minus values are means ±SD. Data are for the on-treatment efficacy population during the randomized treatment period.
† Values were normalized to prednisone equivalents.
‡ P values were calculated with the use of the nonparametric Wilcoxon rank-sum test.

incidence of inhaled glucocorticoid–associated local adverse events with albuterol–budesonide appeared to be higher in the subgroup receiving a SABA alone at baseline than in the subgroup receiving a SABA plus a low-dose inhaled glucocorticoid or leukotriene-receptor antagonist. Because the incidence of inhaled glucocorticoid–associated local adverse events among trial participants who had been receiving a low-dose inhaled glucocorticoid was more balanced between the albuterol–budesonide and albuterol groups, this finding is probably due to the introduction of an inhaled glucocorticoid in participants who had been receiving a SABA only, which led to an increased likelihood of inhaled glucocorticoid–associated local adverse events. Overall, the percentage of participants who discontinued the trial drug owing to adverse events was low in both treatment groups.

Other studies have investigated fixed-dose, inhaled glucocorticoid–containing rescue therapy as compared with SABA rescue therapy in patients with mild asthma, including trials of inhaled glucocorticoid–formoterol rescue therapy[11,12] and as-needed inhaled glucocorticoid–albuterol.[13] Each showed a lower likelihood of exacerbations with combination rescue therapy. The results of a recent systematic review and meta-analysis of randomized trials in any type of asthma showed that rescue therapy with combination inhaled glucocorticoid–formoterol or inhaled glucocorticoid–SABA was associated with better asthma control and fewer exacerbations than a SABA only.[14] Together with the findings of the BATURA trial, these results support the use of inhaled glucocorticoid–containing rescue therapy for persons treated for mild asthma.

A strength of our trial is its fully decentralized design, making it one of the first virtual trials in asthma.[15] The benefits of a decentralized trial design for patients include removal of logistic barriers and improved access, comfort, and convenience, with decentralized trials allowing participants to accommodate trial-related activities around their daily lives, resulting in lowered participant burden, including travel burden.[16,17] The benefits for researchers include efficiency and the possibility of enrolling patients who are typically underrepresented in conventional trials owing to distance from trial sites, physical difficulties,

Table 3. Adverse Events (Safety Analysis Population).*

Event	Albuterol–Budesonide (N=1209)	Albuterol (N=1212)
	no. of participants (%)	
Any adverse event	510 (42.2)	527 (43.5)
Events occurring in ≥2% of participants in either group		
Upper respiratory tract infection	65 (5.4)	73 (6.0)
Coronavirus disease 2019	63 (5.2)	67 (5.5)
Nasopharyngitis	45 (3.7)	32 (2.6)
Sinusitis	38 (3.1)	30 (2.5)
Bronchitis	29 (2.4)	32 (2.6)
Cough	30 (2.5)	29 (2.4)
Influenza	26 (2.2)	21 (1.7)
Asthma	17 (1.4)	25 (2.1)
Any serious adverse event	37 (3.1)	37 (3.1)
Any adverse event leading to treatment discontinuation	15 (1.2)	33 (2.7)
Any treatment-related adverse event†	50 (4.1)	48 (4.0)
Any adverse event with an outcome of death‡	1 (0.1)	1 (0.1)

* The safety analysis population included all the participants who underwent randomization and received at least one actuation of trial treatment, according to the actual treatment received. Data are for events that occurred during the treatment period. The mean (±SD) exposure to trial medication was 258.6±111.19 days in the albuterol–budesonide group and 253.1±113.92 days in the albuterol group.
† Shown are events that were considered by the investigator to be treatment-related.
‡ One death occurred in each group (both deaths were the result of unknown causes). Neither of the deaths was considered by the investigator to be treatment-related.

work and home responsibilities, or socioeconomic status.[16,17] That being said, limitations associated with decentralized studies include the risk of discontinuation because of a lack of patient investment; approximately 19% of the participants were lost to follow-up in the BATURA trial. Of note, a high percentage of participants (approximately 60%) were recruited through social media advertising, which may have also led to increased discontinuation rates, because participants recruited from their treatment clinics or local area may be more likely to maintain trial participation.

Additional limitations include the small number of adolescents (and lack of children), which limits the generalizability of the trial findings to these age groups. Furthermore, participants had disease that was uncontrolled despite treatment for mild asthma, which limits the generalizability of the results to persons with well-controlled asthma. An additional limitation of the decentralized trial is that lung-function assessments were not included, nor were assessments of exhaled nitric oxide and blood eosinophil measurements; these factors prevented an assessment of antiinflammatory effects or predictors of response. Although the lack of lung-function assessment is a limitation and precludes an objective confirmation of the asthma diagnosis, the inclusion of participants with physician-diagnosed asthma may make the trial results more generalizable to clinical settings in which spirometry is not routinely used, including most primary care clinics. Participants in the trial had a median disease duration of 24 years, and 78% had allergens as an asthma trigger, which suggests that their asthma was well established. Finally, stopping a trial early on the basis of treatment superiority at the interim analysis is associated with limitations, including the potential to exaggerate efficacy and truncated evidence for secondary efficacy and safety outcomes.[18]

In this trial, as-needed use of albuterol–budesonide resulted in a lower risk of a severe asthma exacerbation than as-needed use of albu-

terol among participants with disease that was uncontrolled despite treatment for mild asthma.

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