

Safety and Effectiveness of As-Needed Formoterol in Asthma Patients Taking Inhaled Corticosteroid (ICS)-Formoterol or ICS-Salmeterol Maintenance Therapy



Helen Kathryn Reddel, PhD^a, Guy Brusselle, MD^b, Rosa Lamarca, PhD^c, Per Gustafson, MD^d, Gary P. Anderson, PhD^e, and Carin Jorup, MD^f Sydney, NSW, and Melbourne, VIC, Australia; Ghent, Belgium; Barcelona, Spain; and Gothenburg, Sweden

What is already known about this topic? Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP) guidelines recommend inhaled corticosteroid (ICS)-formoterol as the preferred controller and reliever for asthma, either in combination with maintenance ICS-formoterol or (in GINA) alone. However, for patients taking a non-formoterol ICS-long-acting β_2 -agonist as maintenance therapy, the recommended reliever is a short-acting β_2 -agonist (SABA) or (in GINA 2023) combination ICS-SABA.

What does this article add to our knowledge? Exacerbation risk was significantly reduced by as-needed formoterol versus as-needed salbutamol when added to maintenance ICS-formoterol, but not to maintenance ICS-salmeterol. ICS-salmeterol maintenance therapy plus as-needed formoterol resulted in more adverse events leading to discontinuation.

How does this study impact current management guidelines? The present findings do not provide sufficient evidence to change the current clinical recommendation that SABA or ICS-SABA is the appropriate reliever for patients with asthma taking maintenance ICS-salmeterol.

BACKGROUND: As-needed low-dose inhaled corticosteroid (ICS)-formoterol reliever is recommended in patients with asthma prescribed maintenance ICS-formoterol. Clinicians often ask whether ICS-formoterol reliever can be used with other maintenance ICS-long-acting β_2 -agonists. **OBJECTIVE:** To evaluate the safety and effectiveness of as-needed formoterol in patients taking maintenance ICS-formoterol or ICS-salmeterol from the RELIEF study. **METHODS:** RELIEF (SD-037-0699) was a 6-month, open-label study that randomized 18,124 patients with asthma to as-needed formoterol 4.5 μ g or salbutamol 200 μ g on top of maintenance

therapy. This *post hoc* analysis included patients on maintenance ICS-formoterol or ICS-salmeterol ($n = 5436$). The primary safety outcome was a composite of serious adverse events (SAEs) and/or adverse events leading to discontinuation (DAEs); the primary effectiveness outcome was time-to-first exacerbation. **RESULTS:** For both maintenance groups and both relievers, similar numbers of patients had ≥ 1 SAE and/or DAE. In patients taking maintenance ICS-salmeterol, but not ICS-formoterol, significantly more non-asthma-related and nonserious DAEs occurred with as-needed formoterol versus as-needed salbutamol ($P = .0066$ and $P = .0034$, respectively). In patients taking

^aThe Woolcock Institute of Medical Research, The University of Sydney, and Macquarie University, Sydney, Australia

^bDepartment of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

^cBioPharmaceuticals R&D, Late-Stage Development, Respiratory & Immunology, AstraZeneca, Barcelona, Spain

^dBioPharmaceuticals Medical, Respiratory & Immunology, AstraZeneca, Gothenburg, Sweden

^eLung Health Research Centre, Department of Biochemistry and Pharmacology, University of Melbourne, Melbourne, VIC, Australia

^fBioPharmaceuticals R&D, Late-Stage Development, Respiratory & Immunology, AstraZeneca, Gothenburg, Sweden

This paper was supported by AstraZeneca.

Conflicts of interest: H. K. Reddel reports nonfinancial support from AstraZeneca during the conduct of the study; research grants from AstraZeneca, GlaxoSmithKline, and Novartis; personal fees for providing independent medical advice in advisory boards for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Sanofi; independent medical education presentations for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Sanofi, and Teva; and consulting for AstraZeneca and Novartis; she is also Chair of the GINA Scientific Committee and a member of the GINA Board of Directors. R. Lamarca, P. Gustafson, and C.

Jorup are employees and shareholders of AstraZeneca. G. P. Anderson reports consultancy fees and share options from Pieris and ENA respiratory; and consultancy, advisory board, and speaker fees from AstraZeneca, Novartis, GlaxoSmithKline, DevPro, and Menarini. G. Brusselle reports honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, and Teva; he is a member of advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva, and is also a member of the GINA Science Committee and GINA Board of Directors.

Received for publication August 4, 2022; revised March 3, 2023; accepted for publication March 21, 2023.

Corresponding author: Helen Kathryn Reddel, PhD, Woolcock Institute of Medical Research, 431 Glebe Point Rd, Glebe, NSW 2037, Australia. E-mail: helen.reddel@woolcock.org.au.

2213-2198

© 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2023.03.046>

Abbreviations used

AE- Adverse event
CI- Confidence interval
DAE- Discontinuation due to adverse event
GINA- Global Initiative for Asthma
HR- Hazard ratio
ICS- Inhaled corticosteroid
LABA- Long-acting β_2 -agonists
LM- Leukotriene modifiers
MART- Maintenance and reliever therapy
NAEPP- National Asthma Education and Prevention Program
OR- Odds ratio
SABA- Short-acting β_2 -agonists
SAE- Serious adverse event

maintenance ICS-formoterol, there was a significantly lower risk in time-to-first exacerbation with as-needed formoterol versus as-needed salbutamol (hazard ratio [HR]: 0.82, 95% confidence interval [CI]: 0.70, 0.95; $P = .007$). In patients taking ICS-salmeterol maintenance, time-to-first exacerbation was not significantly different between treatment arms (HR: 0.95, 95% CI: 0.84, 1.06; $P = .35$).

CONCLUSIONS: As-needed formoterol significantly reduced exacerbation risk compared with as-needed salbutamol when added to maintenance ICS-formoterol, but not to maintenance ICS-salmeterol. More DAEs were seen with ICS-salmeterol maintenance therapy plus as-needed formoterol. Further research is needed to assess whether this is relevant to as-needed combination ICS-formoterol. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2023;11:2104-14)

Key words: Asthma; Budesonide-formoterol; Effectiveness; Exacerbations; Formoterol; ICS; Reliever; Safety; Salbutamol; Salmeterol

In patients with moderate-to-severe asthma, taking inhaled corticosteroids (ICS) in combination with formoterol, a rapid-onset long-acting β_2 -agonist (LABA) as maintenance and reliever therapy (called MART, or single inhaler MART (SMART)) significantly reduces the risk of severe exacerbations compared with ICS-LABA maintenance plus a short-acting β_2 -agonist (SABA)¹ and compared with conventional best practice plus SABA reliever.^{2,3} In addition, patients with mild asthma taking as-needed ICS-formoterol as their only therapy have a substantial reduction in risk of severe exacerbations compared with those taking as-needed SABA alone and similar protection as, or greater protection than, patients taking budesonide maintenance with as-needed SABA.⁴⁻⁸

The 2023 Global Initiative for Asthma (GINA) report recommends as-needed low-dose ICS-formoterol as the preferred (Track 1) reliever option for patients aged ≥ 12 years at all treatment steps, either alone at Steps 1 and 2 or with maintenance ICS-formoterol as controller at Steps 3 to 5 (ie, MART), and with MART as one of three options in Steps 3 and 4 for patients aged 6 to 11 years.^{9,10} MART with ICS-formoterol is also the preferred treatment option for patients aged ≥ 4 years at Steps 3 and 4 in the 2020 focused updates to the National

Asthma Education and Prevention Program (NAEPP) guidelines.¹¹ For patients taking nonformoterol ICS-LABA as maintenance therapy, the reliever recommended by both GINA and NAEPP is a SABA such as salbutamol or, in GINA 2023, a combination ICS-SABA.⁹⁻¹¹ However, some clinicians have asked if it would be safe and effective for patients receiving nonformoterol ICS-LABA maintenance treatment to use ICS-formoterol as reliever therapy.

To answer this question, a literature search was undertaken to identify any randomized controlled trials of as-needed formoterol or as-needed ICS-formoterol as reliever in patients receiving maintenance nonformoterol LABA-containing medications (see this article's Online Repository at www.jaci-inpractice.org). Of the 38 randomized controlled trials in asthma yielded by the search, the only relevant study identified was RELIEF (SD-037-0699),¹² an open-label study conducted between April 2000 and June 2001 that assessed the safety and real-world effectiveness of as-needed formoterol versus as-needed salbutamol in patients with asthma using reliever medication with or without maintenance treatment, including maintenance therapies containing ICS and LABA.¹² The study demonstrated that as-needed formoterol had a similar safety profile to and increased asthma control compared with as-needed salbutamol, with fewer asthma exacerbations and less maintenance and as-needed reliever medication use.¹² Although only ICS-formoterol (and not formoterol alone) is now recommended for clinical use as a reliever,^{9,11} the data from this study provided the opportunity to assess the safety and effectiveness of the formoterol component, when used as a reliever.

Using the data from the RELIEF study, we conducted a *post hoc* analysis to evaluate the safety and effectiveness of as-needed formoterol versus as-needed salbutamol in patients with asthma aged ≥ 6 years taking ICS-LABA (salmeterol or formoterol) as background maintenance therapy.

METHODS

Study design

The study design of the RELIEF trial has been previously described in detail.¹² Briefly, the open-label, randomized, parallel-group, real-world study was conducted at 1139 centers in 24 countries. A total of 18,124 patients aged ≥ 6 years were recruited from general practice and specialist centers. They were required to have a clinical diagnosis of asthma and to be currently using, or be candidates to receive, a β_2 -agonist as reliever medication. Patients were permitted to use any standard asthma therapy as maintenance treatment. Changes in prescribed medication and emergency treatment according to local procedures were also permitted. Eligible patients were randomized to reliever treatment with either (1) 1 inhalation as needed of formoterol Turbuhaler 4.5 μg (delivered dose) or (2) 1 inhalation as needed of salbutamol 200 μg by a pressurized metered-dose inhaler (18 countries) or the equivalent salbutamol dose by a dry powder inhaler (1 $\times$ 200 μg inhalation by Diskus/Diskhaler [3 countries] or 1 $\times$ 100 μg inhalation via Turbuhaler¹³ [3 countries]). Adults and children 6 to 11 years of age were advised not to exceed 12 and 8 inhalations of their reliever inhaler in 24 hours, respectively. If patients were taking regular LABA treatment, the daily limit of reliever medication was reduced so that adults randomized to formoterol would receive no more than 54 μg of formoterol equivalents (72 μg metered dose) in a day (36 μg and 48 μg , respectively, for children). If they had exceeded the

limit in any day, they were asked to contact the investigator, who would decide on appropriate actions. Patients attended the clinic at study entry and after 1, 3, and 6 months of treatment, and asthma maintenance treatment was recorded at study entry and at the final visit. Spontaneously reported and/or observed adverse events (AEs), serious AEs (SAEs), discontinuation due to AEs (DAEs), health care resource utilization, and change in maintenance asthma medication were registered in a paper diary by the patient throughout the study (visits 1–4) and were recorded by the investigator at each clinic visit. Patients also recorded the number of inhalations of reliever medication and number of days with asthma symptoms in their paper diaries during the last 2 weeks before visits 2, 3, and 4. No information on adherence or duration of maintenance treatment was recorded; patients who reported the same medication at entry and at the final visit were considered to be on that medication over the 6 months of follow-up.

Asthma severity

In the original study, the type of asthma maintenance medication recorded at visit 1 was used to categorize patients by severity according to then-current GINA recommendations as follows: patients using ICS at a daily dose of <500 μg (beclomethasone equivalent) or use of LABA, cromoglycate, nedocromil, theophylline, leukotriene modifiers (LM), or other asthma medication including SABA, antihistamines, and anticholinergics, were described as having mild asthma; patients using ICS at a daily dose of ≥ 500 μg or a daily dose of 500 to 800 μg plus LABA, theophylline, or LM were described as having moderate asthma; and patients using ICS at a daily dose of >800 μg plus LABA, theophylline, LM, or systemic corticosteroids were described as having severe asthma. Fluticasone propionate 250 μg and beclomethasone 500 μg were considered equipotent to budesonide 400 μg .

Post hoc analysis

For the purpose of this *post hoc* analysis and to answer the clinical question of interest, only patients taking maintenance ICS-LABA therapy at study entry were included. Of all patients included in the RELIEF study, 95% of those taking formoterol and 96% of those taking salmeterol were also taking ICS (hereafter referred to as ICS-formoterol and ICS-salmeterol) as either a fixed-dose combination or via separate inhalers. For patients taking ICS-formoterol at study entry, budesonide was the most common ICS ($n = 1464$, 68.3%), and for patients taking ICS-salmeterol at study entry, the most common ICS was fluticasone propionate ($n = 2215$, 67.2%).

Outcomes

The primary safety variables, as for the original study, were asthma-related and non-asthma-related SAEs and DAEs, and incidence of an AE (defined as the number of subjects with at least 1 SAE or DAE). An SAE was defined as any event causing death, any life-threatening condition, hospitalization or prolongation of hospitalization, or persistent or significant disability or congenital abnormality.¹⁴ Asthma-related events were events including “asthma aggravated symptoms” or “asthma not otherwise specified.” Cardiovascular-related SAEs and DAEs coded in the System Organ Class “Cardiac disorders” or by the Preferred Term “Sudden cardiac death” within the System Organ Class “General disorders and administration site conditions” were also reported, as cardiovascular events are potential class effects of the β_2 -agonists formoterol, salmeterol, and salbutamol.¹⁵

The primary effectiveness variable was time-to-first exacerbation. The RELIEF study predated the joint American Thoracic Society/

European Respiratory Society Task Force standardized definition of exacerbations,¹⁶ and an exacerbation was defined by one or more of the following: (1) any increase in maintenance asthma medication due to deterioration in asthma, (2) a course of oral corticosteroids lasting ≥ 5 days, (3) emergency treatment with nebulized β_2 -agonist or corticosteroid injection, or (4) hospitalization, all due to deterioration of asthma. Any event of 2, 3, or 4 was classed as a severe exacerbation.¹² Secondary efficacy variables were reliever medication use and symptom days.

Statistical analysis

The primary safety variables, number of subjects with non-asthma-related and asthma-related SAEs and DAEs, were analyzed using a logistic regression model with treatment (as-needed formoterol or as-needed salbutamol) as a factor and expressed as odds ratios (ORs) within each stratum (ICS-formoterol and ICS-salmeterol). The following SAE subcategories were analyzed based on the same logistic regression model: asthma-related, non-asthma-related, and cardiovascular-related, as defined above. DAEs were divided into asthma-related and non-asthma-related DAEs, DAEs due to serious AEs, and DAEs due to non-serious AEs. AEs representing potential β_2 -agonist effects were summarized descriptively. The number of overall and severe exacerbations was presented by stratum, as defined above, treatment, and change in ICS (yes/no) from study entry to the final visit. A Cox regression model with treatment, stratum, and treatment by stratum interaction as factors was carried out for time-to-first event (SAE or DAE), time-to-first asthma exacerbation, and time-to-first severe asthma exacerbation. Results were expressed as hazard ratios (HRs). The use of reliever medication and percentage of days with asthma symptoms was analyzed using a mixed model for repeated measures, including treatment period as a fixed effect and subject as a random effect for each stratum. There was no control for type I error; a nominal alpha of 0.05 was used for interpretation of significance.

RESULTS

Subgroup definition

The RELIEF study recruited 18,124 patients; of these, 9064 were randomized to as-needed formoterol and 9060 to as-needed salbutamol. At enrolment, regular ICS and LABA were used by 5436 (30%) patients, with a mean daily budesonide-equivalent ICS dose of 947 μg . Of these 5436 patients with asthma, 2142 (39.4%) were using ICS-formoterol and 3294 (60.6%) were using ICS-salmeterol as maintenance treatment. The following subgroups were identified for analysis: maintenance ICS-formoterol + as-needed formoterol ($n = 1044$), maintenance ICS-formoterol + as-needed salbutamol ($n = 1098$), maintenance ICS-salmeterol + as-needed formoterol ($n = 1605$), and maintenance ICS-salmeterol + as-needed salbutamol ($n = 1689$) (Figure 1).

Baseline demographics and patient disposition

Baseline characteristics for patients randomized to as-needed formoterol or as-needed salbutamol were similar in both maintenance ICS-LABA subgroups (Table I). A higher proportion of patients in the maintenance ICS-formoterol subgroup had mild and moderate disease (based on treatment level) compared with the maintenance ICS-salmeterol subgroup (mild: 22.2% vs 17.9%; moderate: 46.6% vs 39.6%), whereas a greater proportion of patients in the maintenance ICS-salmeterol subgroup had

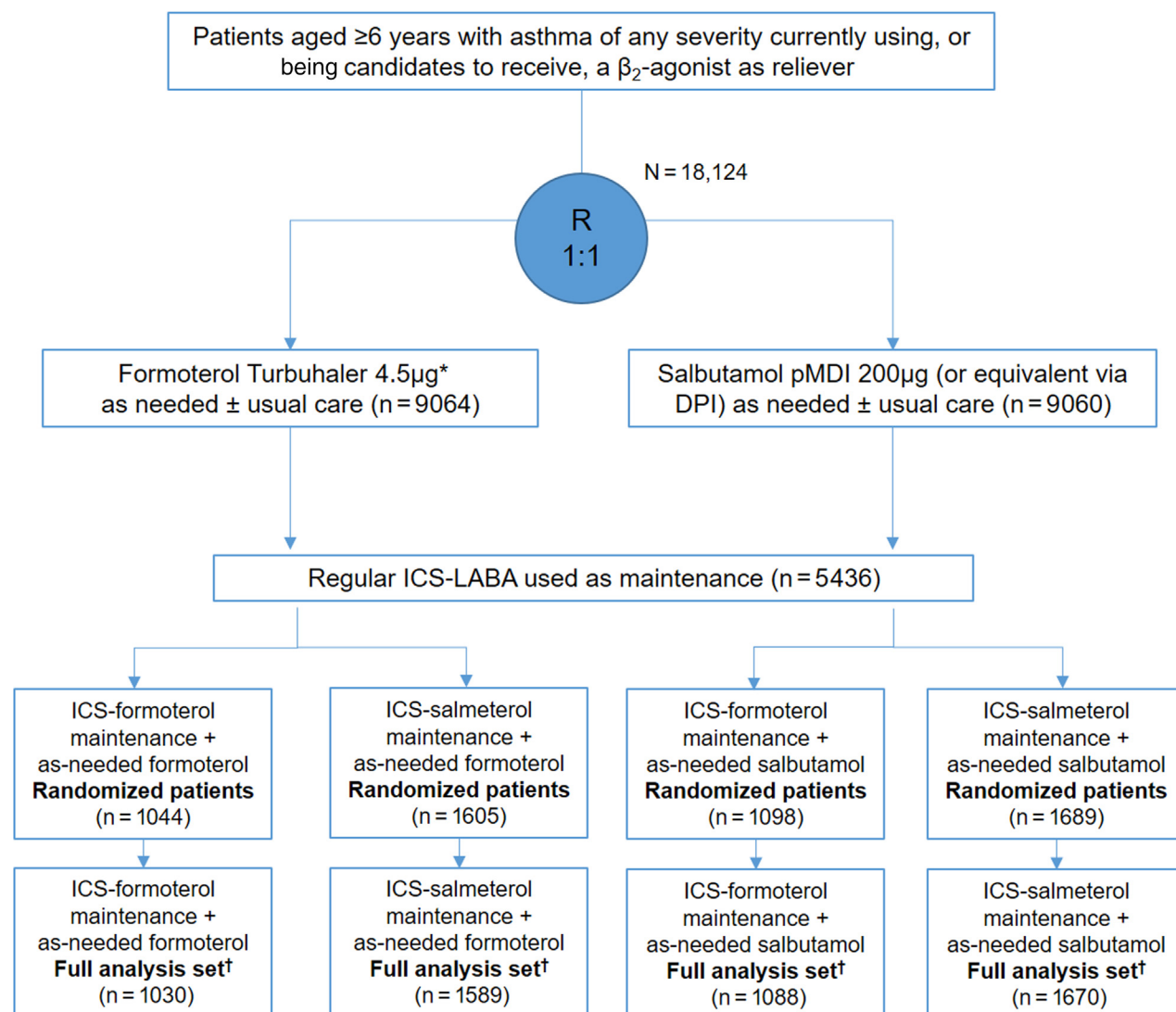


FIGURE 1. Patient flow and subgroup definition for this analysis. *Delivered dose. †The full-analysis set only included randomized patients who received treatment. *DPI*, dry powder inhaler; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *pMDI*, pressurized metered-dose inhaler; *R*, randomization.

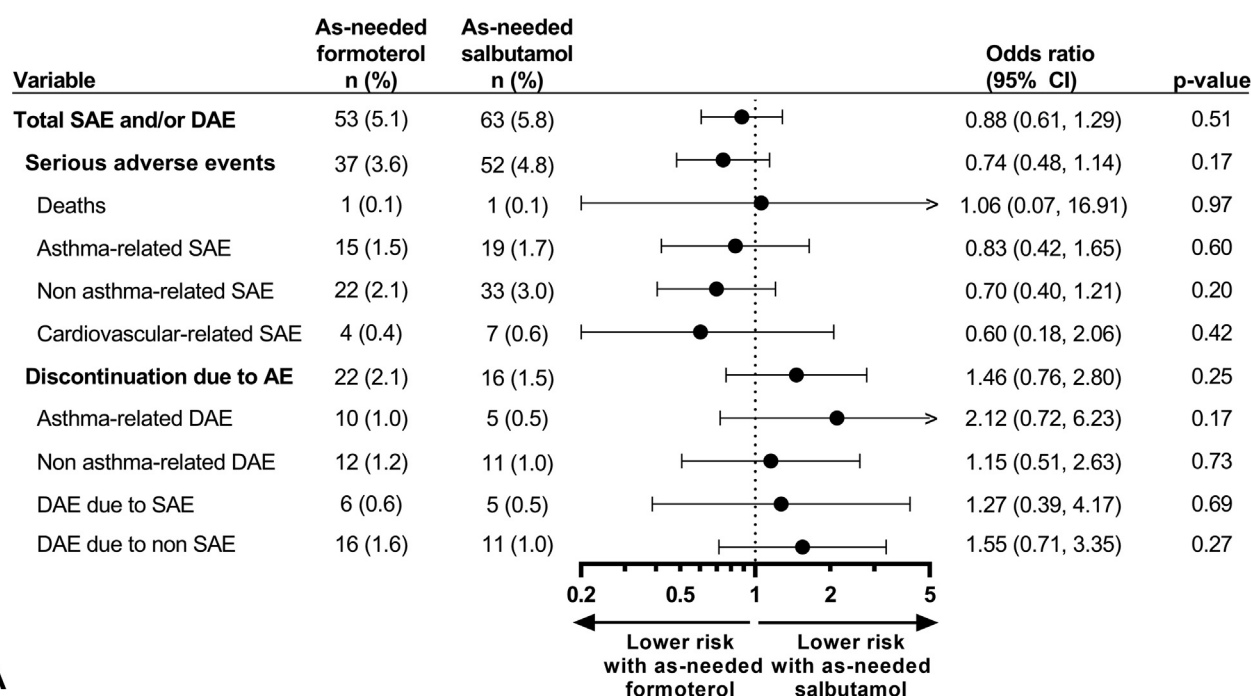
TABLE I. Baseline characteristic of patients by medication use

Background treatment	Maintenance ICS-formoterol bid			Maintenance ICS-salmeterol bid		
	As-needed formoterol (n = 1044)	As-needed salbutamol (n = 1098)	All (n = 2142)	As-needed formoterol (n = 1605)	As-needed salbutamol (n = 1689)	All (n = 3294)
Age, mean (SD) (y)	44.4 (17.4)	43.8 (17.4)	44.1 (17.4)	43.8 (18.4)	43.4 (18.2)	43.6 (18.3)
Children (%)	2.7	2.6	2.6	3.9	3.7	3.8
Adolescents (%)	3.8	4.8	4.3	6.9	7.0	7.0
Female (%)	59.3	64.2	61.8	59.9	59.7	59.8
Regular smoker (%)	14.6	15.4	15.0	15.7	15.2	15.5
Asthma medication level* (%)						
Mild	22.1	22.2	22.2	17.1	18.7	17.9
Moderate	46.6	46.7	46.6	40.1	39.0	39.6
Severe	31.3	31.1	31.2	42.8	42.3	42.6

bid, twice daily; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *LM*, leukotriene modifier; *LTRA*, leukotriene receptor antagonist; *SABA*, short-acting β_2 -agonist; *SCS*, systemic corticosteroid; *SD*, standard deviation; *y*, years.

*Classification as in the original RELIEF study, based on maintenance treatment. Mild: use of ICS at a daily dose of <500 µg or use of LABA, cromoglycate, nedocromil, theophylline, LM, or other asthma medication including SABA, antihistamines, and anticholinergics. Moderate: use of ICS at a daily dose of ≥500 µg or a daily dose of 500 to 800 µg and LABA/theophylline or LM. Severe: use of ICS at a daily dose of >800 µg and use of LABA, theophylline, LTRA, or SCS.

Patients receiving maintenance ICS-formoterol at study entry



Patients receiving maintenance ICS-salmeterol at study entry

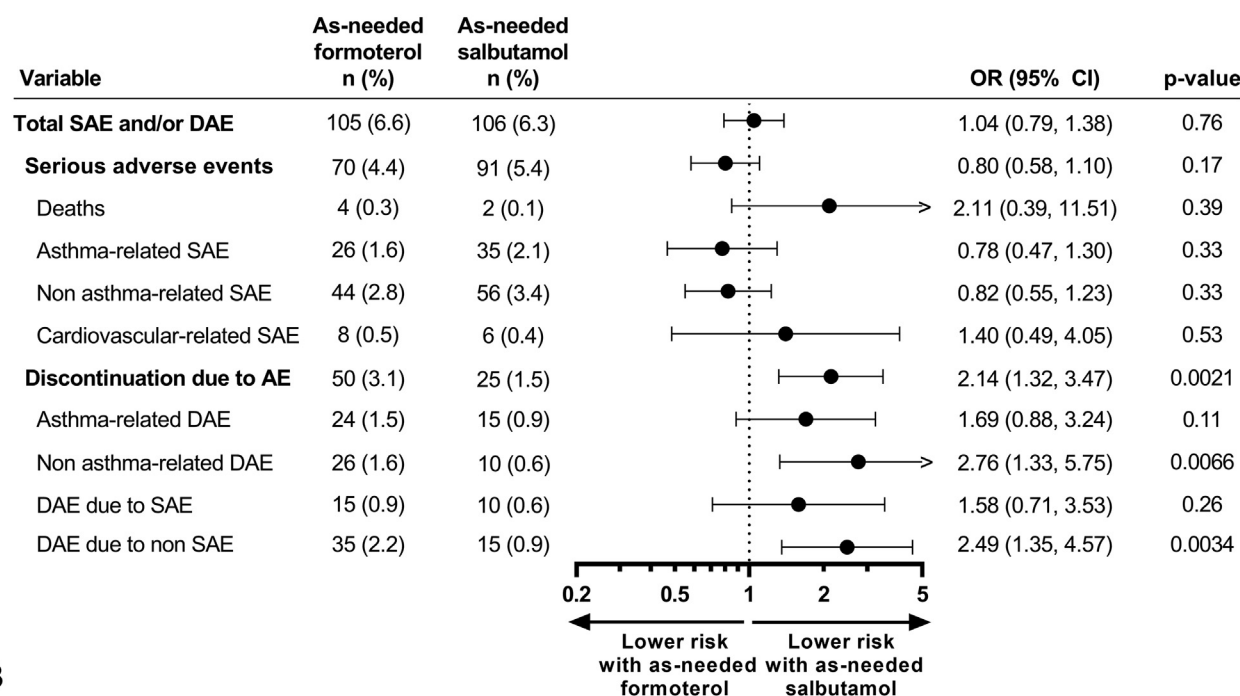


FIGURE 2. Percentage of patients with at least 1 SAE or DAE and odds ratios by (A) maintenance ICS-formoterol at study entry and (B) maintenance ICS-salmeterol at study entry. The arrowheads indicate that the upper limit extends above the x-axis range. AE, adverse event; CI, confidence interval; DAE, discontinuation due to adverse event; ICS, inhaled corticosteroid; OR, odds ratio; SAE, serious adverse event.

TABLE II. Incidence of SAEs and DAEs by as-needed medication and type of maintenance ICS-LABA at study entry

Type of SAE/DAE	As-needed formoterol		As-needed salbutamol	
	Maintenance ICS-formoterol (n = 1030)	Maintenance ICS-salmeterol (n = 1589)	Maintenance ICS-formoterol (n = 1088)	Maintenance ICS-salmeterol (n = 1670)
All SAEs, n (%)				
Asthma-related SAEs	15 (1.5)	26 (1.6)	19 (1.7)	35 (2.1)
Non-asthma-related SAEs	22 (2.1)	44 (2.8)	33 (3.0)	56 (3.4)
Cardiovascular SAEs	4 (0.4)	8 (0.5)	7 (0.6)	6 (0.4)
All DAEs, n (%)				
DAE due to SAE	6 (0.6)	15 (0.9)	5 (0.5)	10 (0.6)
DAE due to non-serious AE	16 (1.6)	35 (2.2)	11 (1.0)	15 (0.9)
CV-related DAE, n (%)				
CV DAE due to SAE	2 (0.2)	4 (0.3)	1 (0.1)	2 (0.1)
CV DAE due to non-serious AE	2 (0.2)	3 (0.2)	0	0
Non-CV-related DAE, n (%)				
Non-CV DAE due to SAE	4 (0.4)	11 (0.7)	4 (0.4)	8 (0.5)
Non-CV DAE due to non-serious AE	14 (1.4)	32 (2.0)	11 (1.0)	15 (0.9)

Numbers of cardiovascular and non-cardiovascular events were too small for statistical analysis.

In MedDRA, cardiovascular AEs were those coded in the System Organ Class of “Cardiac disorders” or by the Preferred Term “Sudden cardiac death” within the System Organ Class of “General disorders and administration site conditions.”

AE, adverse event; CV, cardiovascular; DAE, discontinuation due to adverse event; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

severe asthma (42.6% vs 31.2%) (Table I and Table E1, available in this article’s Online Repository at www.jaci-inpractice.org).

Safety

Overall, the odds of experiencing an SAE and/or DAE (combined) during the treatment period were similar between as-needed formoterol and as-needed salbutamol in patients taking maintenance ICS-formoterol (OR: 0.88, 95% confidence interval [CI]: 0.61, 1.29; $P = .51$) and maintenance ICS-salmeterol (OR: 1.04, 95% CI: 0.79, 1.38; $P = .76$) at study entry (Figure 2).

Serious adverse events. In patients taking maintenance ICS-formoterol at study entry, there was no significant difference between as-needed formoterol and as-needed salbutamol in the incidence of SAEs (OR: 0.74, 95% CI: 0.48, 1.14; $P = .17$), asthma-related SAEs (OR: 0.83, 95% CI: 0.42, 1.65; $P = .60$), non-asthma-related SAEs (OR: 0.70, 95% CI: 0.40, 1.21; $P = .20$), or cardiovascular-related SAEs (OR: 0.60, 95% CI: 0.18, 2.06; $P = .42$) (Figure 2, A). Similar findings were observed in patients taking maintenance ICS-salmeterol at study entry (SAEs: OR: 0.80, 95% CI: 0.58, 1.10; $P = .17$; asthma-related SAEs: OR: 0.78, 95% CI: 0.47, 1.30; $P = .33$; non-asthma-related SAEs: OR: 0.82, 95% CI: 0.55, 1.23; $P = .33$; cardiovascular-related SAEs: OR: 1.40, 95% CI: 0.49, 4.05; $P = .53$) (Figure 2, B). The odds of reporting any cardiovascular-related AE (serious or nonserious) were similar across as-needed treatment arms, regardless of maintenance therapy (ICS-formoterol: OR: 1.00, 95% CI: 0.53, 1.89; $P = .99$; ICS-salmeterol: OR: 1.19, 95% CI: 0.68, 2.10; $P = .54$). There was a total of 8 deaths (0.15%) (see this article’s Online Repository at www.jaci-inpractice.org).

Discontinuation due to adverse events. The odds of DAE were similar between as-needed formoterol and as-needed

salbutamol in patients taking ICS-formoterol maintenance at study entry (OR: 1.46, 95% CI: 0.76, 2.80; $P = .25$) (Figure 2, A). However, in patients taking maintenance ICS-salmeterol at study entry, the odds of discontinuing their treatment due to an AE were higher in those randomized to as-needed formoterol than those randomized to as-needed salbutamol (OR: 2.14, 95% CI: 1.32, 3.47; $P = .002$). The differences in DAEs were significant for DAEs due to nonserious AEs (OR: 2.49, 95% CI: 1.35, 4.57; $P = .003$) and for non-asthma-related DAEs (OR: 2.76, 95% CI: 1.33, 5.75; $P = .007$) (Figure 2, B). Numbers of cardiovascular and noncardiovascular DAEs (Table II) were too small for formal statistical analysis.

Similar results were seen for the time-to-first safety outcome. Time-to-first SAE and/or DAE (combined) was similar for as-needed formoterol and as-needed salbutamol in patients taking maintenance ICS-formoterol (HR: 0.89, 95% CI: 0.62, 1.28; $P = .53$) and patients taking maintenance ICS-salmeterol (HR: 1.05, 95% CI: 0.80, 1.37; $P = .72$) at study entry (Figure 3). However, time-to-first DAE and time-to-first non-asthma-related DAE were significantly shorter with as-needed formoterol compared with as-needed salbutamol when used on top of maintenance ICS-salmeterol (HR: 2.12, 95% CI: 1.31, 3.43; $P = .002$ and HR: 2.76, 95% CI: 1.33, 5.72; $P = .006$, respectively). There was no notable difference in time-to-first asthma-related DAE (Figures 3 and 4).

The most common non-serious DAEs were aggravation of asthma (0.6%–1.2%), cough (0%–0.1%), and dizziness (0%–0.1%). The most common serious DAEs were myocardial infarction (0%–0.2%) and lower respiratory tract infection (0%–0.1%).

Effectiveness

The risk of experiencing any exacerbation was lower in patients randomized to as-needed formoterol versus as-needed salbutamol in patients taking maintenance ICS-formoterol at study entry (HR: 0.82, 95% CI: 0.70, 0.95; $P = .007$), but not

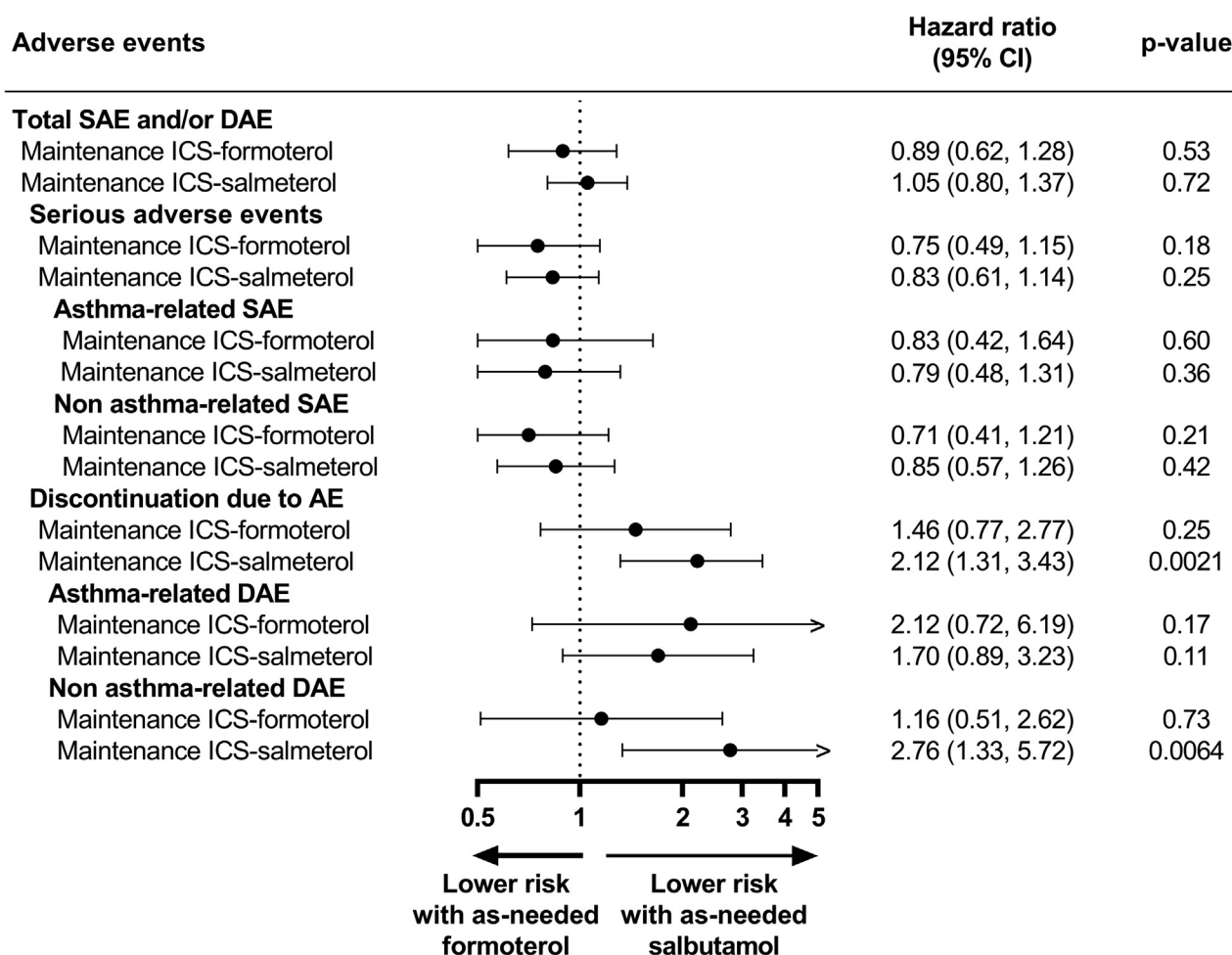


FIGURE 3. Time-to-first SAE or DAE with as-needed formoterol versus as-needed salbutamol by use of maintenance ICS-formoterol or maintenance ICS-salmeterol at study entry. A hazard ratio of less than 1 favors formoterol. The arrowheads indicate that the upper limit extends above the x-axis range. AE, adverse event; CI, confidence interval; DAE, discontinuation due to adverse event; ICS, inhaled corticosteroid; SAE, serious adverse event.

significantly different between treatment arms in those taking maintenance ICS-salmeterol at study entry (HR: 0.95, 95% CI: 0.84, 1.06; $P = .35$ [HR <1 indicates a lower risk with as-needed formoterol]) (Figure 5, A). There was no significant difference in the risk of experiencing a severe exacerbation between patients randomized to as-needed formoterol versus as-needed salbutamol in either ICS-LABA maintenance group (ICS-formoterol maintenance: HR: 0.85, 95% CI: 0.70, 1.05; $P = .13$; ICS-salmeterol maintenance: HR: 0.99, 95% CI: 0.85, 1.16; $P = .94$) (Figure 5, B).

Reliever use, calculated as average doses per day, was significantly lower with as-needed formoterol compared with as-needed salbutamol when used on top of ICS-formoterol maintenance, but the differences were small (approximately 0.2 doses/d), with no notable difference in patients taking ICS-salmeterol maintenance (Table III).

There was no notable difference in asthma symptom days between reliever medications in patients taking either ICS-formoterol or ICS-salmeterol maintenance therapy (Table III).

DISCUSSION

As-needed ICS-formoterol is the preferred controller and reliever therapy for adults and adolescents at all treatment steps in the GINA 2023 Strategy Report, either with maintenance ICS-formoterol (i.e., MART) in GINA Steps 3–5, or without any maintenance treatment in GINA Steps 1 and 2). MART with ICS-formoterol is also an option at GINA Steps 3 and 4 for children aged 6 to 11 years.^{9,17} In the 2020 focused update of NAEPP guidelines, MART with ICS-formoterol is also the preferred treatment for Steps 3 and 4 in patients aged ≥4 years.¹¹ Both GINA and the NAEPP guidelines recommend against the use of ICS-formoterol as reliever in patients taking combination non-formoterol ICS-LABA maintenance therapy, citing lack of data for the safety, efficacy, or effectiveness of such treatment,^{9–11} but clinicians still ask whether it can be done. It is therefore important to determine any potential safety issues with, and potential therapeutic advantages of, taking as-needed ICS-formoterol on top of maintenance nonformoterol-containing ICS-LABA medications. Following a

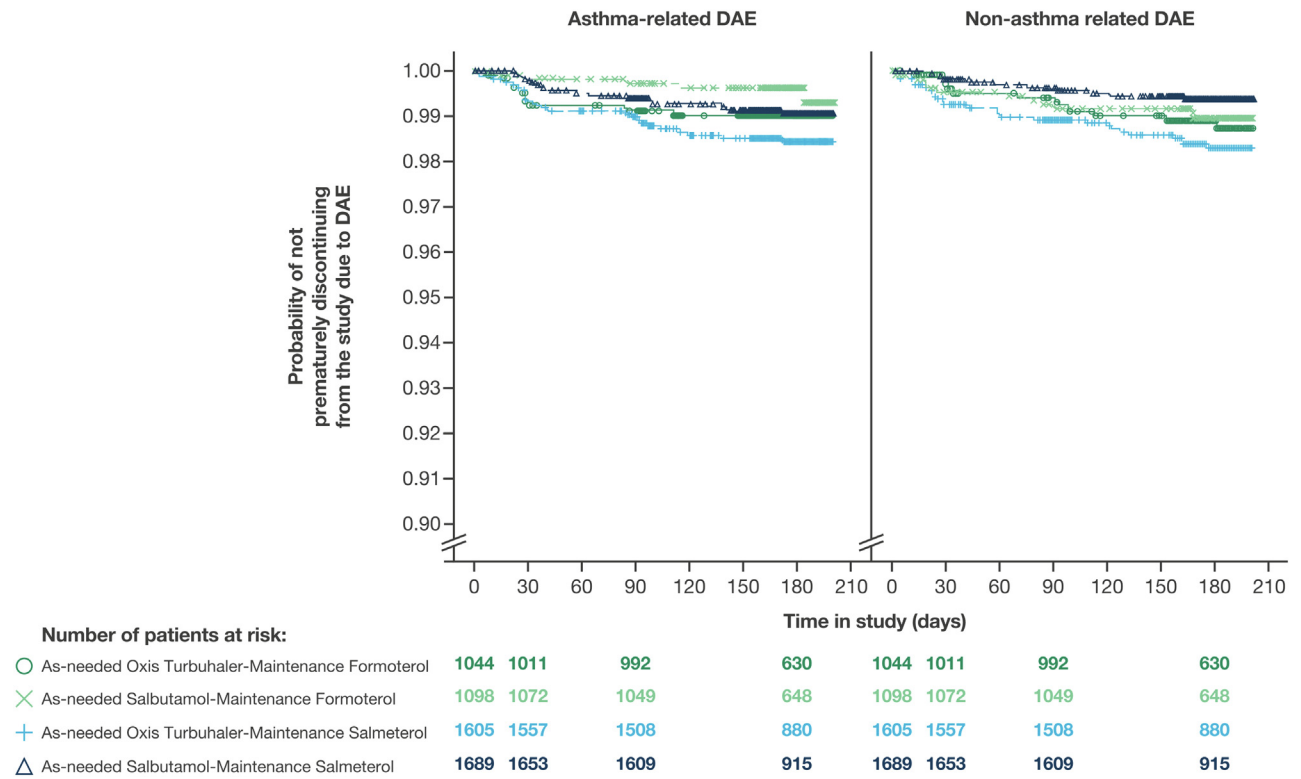


FIGURE 4. Kaplan-Meier plots showing time to premature discontinuation from the study due to AE by asthma relationship (asthma-related and non-asthma-related DAE). Odds ratios are shown in Figure 3. AE, adverse event; DAE, discontinuation due to adverse event.

comprehensive literature search, the RELIEF study was the only randomized controlled trial that would enable us to investigate this important clinical question, albeit only for the formoterol component of the ICS-formoterol reliever.

In this *post hoc* analysis of the RELIEF study, as-needed formoterol showed greater effectiveness compared with as-needed salbutamol when used on top of maintenance ICS-formoterol, whereas there was similar effectiveness between reliever therapies in patients on maintenance ICS-salmeterol therapy. The total incidence of SAEs and DAEs was similar for as-needed formoterol and as-needed salbutamol, irrespective of background maintenance therapy. However, patients taking maintenance ICS-salmeterol who were randomized to as-needed formoterol were more likely to discontinue their treatment due to an AE than patients randomized to as-needed salbutamol. Studies in other fields have shown that in open-label studies, discontinuations are more likely to be reported in patients randomized to an unfamiliar, rather than a familiar, medication.^{18,19}

When taken as reliever on top of ICS-formoterol maintenance, the use of as-needed formoterol resulted in a lower risk of experiencing an exacerbation compared with as-needed salbutamol, and patients using as-needed formoterol as reliever were less likely than those on as-needed salbutamol to experience a first exacerbation. This is consistent with the findings from the subsequent double-blind SMILE study, which showed that, among patients taking maintenance budesonide-formoterol, use of as-needed formoterol as reliever reduced the risk of severe exacerbations compared with as-needed SABA (terbutaline).¹⁴

However, in RELIEF, among patients taking ICS-salmeterol as maintenance therapy, the use of as-needed formoterol and as-needed salbutamol resulted in a similar time-to-first exacerbation.

There may be pharmacological reasons for the observed differences because, at the molecular level, formoterol and salmeterol do not activate the β_2 -adrenoceptor in the same way. The most likely reason could be their marked differences in pharmacological efficacy, a measure of how efficiently they activate signal transduction to ultimately lengthen airway smooth muscle. Conventionally, almost all β_2 -adrenoceptor agonists engage very similar binding domains in the active site and do not bind irreversibly; thus their actions are additive when used together. Salmeterol, however, was specifically designed to have an extremely innovative and unconventional mode of binding to the β_2 -adrenoceptor; its long, highly lipophilic side chain inserts deep into the core of the receptor engaging serine 164 at a so-called exosite to form an irreversible complex.²⁰ Salmeterol, like its parent compound salbutamol to which, structurally, it is very closely related, belongs to the saligenin chemical class; all saligenins are “partial agonists” that have low efficacy. *In vitro* this means that formoterol, which has a very high pharmacological efficacy, relaxes human airway smooth muscle more extensively.²¹ Consequently, increasing doses of formoterol are also more effective than salmeterol in preventing contraction, so called bronchoprotection, when assessed in humans.²² These properties, intrinsic to the structure of different agonists, may help to explain why formoterol offers greater protection from exacerbations than SABA.^{12,14,23} Low-efficacy partial agonists can also be shown to behave as antagonists, and this blocking

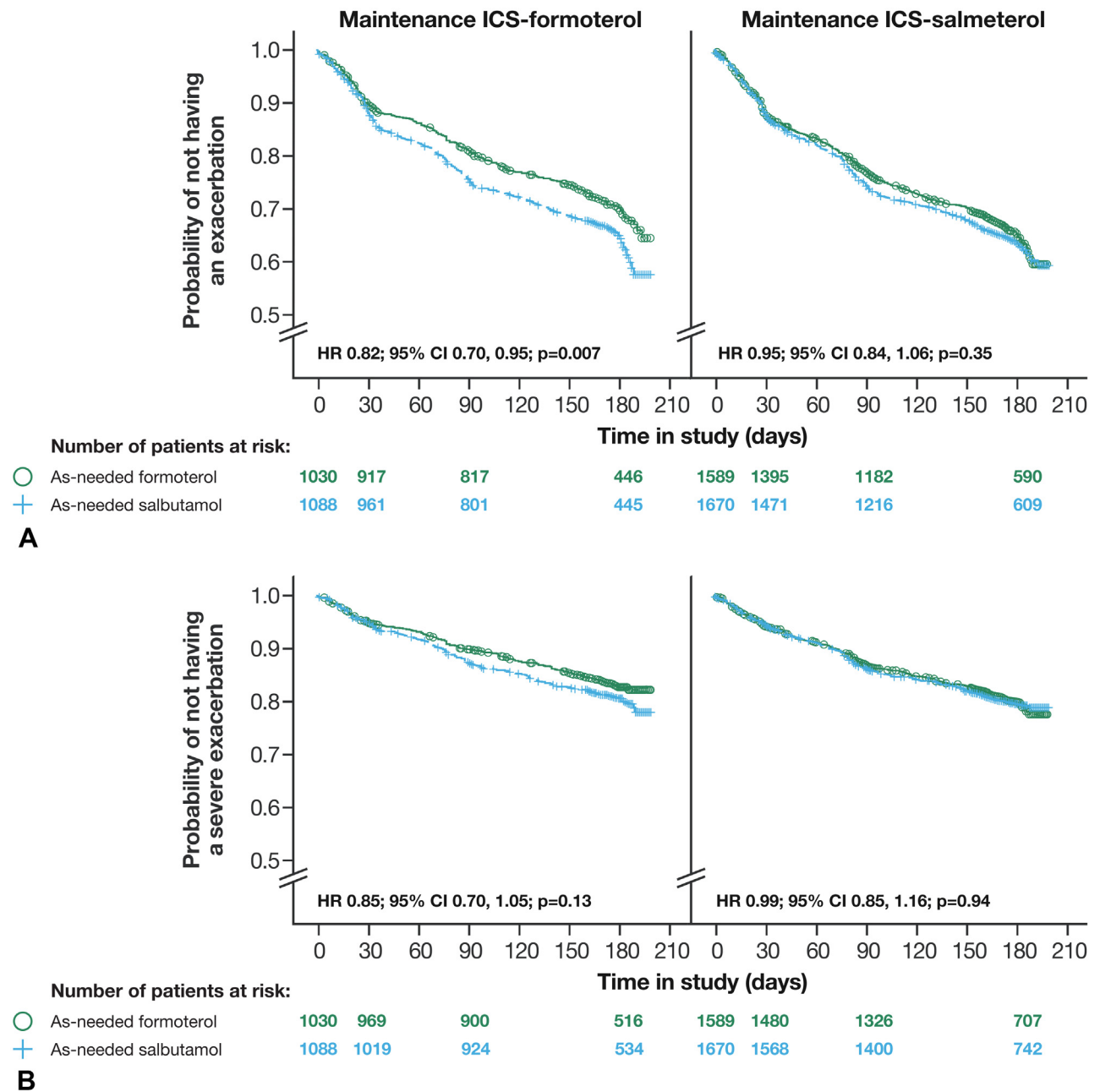


FIGURE 5. Kaplan-Meier plots showing (A) the time-to-first asthma exacerbation and (B) the time-to-first severe asthma exacerbation by as-needed formoterol or as-needed salbutamol and by the type of ICS-LABA maintenance therapy at study entry. *CI*, confidence interval; *HR*, hazard ratio; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist.

effect has been formally demonstrated on human airway smooth muscle *in vitro*.²⁴ However, an emergency department study found no evidence that maintenance salmeterol blocked the effect of a second agonist (albuterol) during acute asthma exacerbations.²⁵ The doses of β_2 -adrenoceptor agonist used in clinical medicine probably occupy only 1% to 3% of all β -receptors on human airway smooth muscle, leaving abundant so-called spare receptors available to a second reliever drug to produce rescue bronchodilation.²⁶ Similarly, it is highly unlikely that differential β_2 -adrenoceptor downregulation could explain the present results because salmeterol and formoterol lead to a very similar

degree of downregulation that is small and stable, albeit mostly due to slightly different mechanisms.^{27,28} Moreover, ICS offer considerable protection from downregulation.²⁹ As the β_2 -adrenoceptor is genetically polymorphic, it is conceivable that subtle genetic variations could be related, but the clinical safety and effectiveness of both formoterol and salmeterol are not related to the β_2 -adrenoceptor haplotype.^{30,31} However, a clinically important difference in clinical outcomes in patients randomized by β -receptor genotype was seen with salbutamol.³² It is also conceivable that there may be unknown effects related to signaling intermediates such as G proteins, arrestins, or cAMP-

TABLE III. Analysis of study reliever medication use and asthma symptoms for each ICS-LABA at study entry

Variable	Maintenance at study entry	Period (mo)	LS means (95% CI)		Estimate for difference	95% CI	P value
			As-needed formoterol	As-needed salbutamol			
Use of study reliever medication (doses/d)	Maintenance ICS-formoterol	1	1.10 (1.00, 1.20)	1.30 (1.20, 1.39)	−0.197	−0.336, −0.057	.006
		3	1.05 (0.95, 1.16)	1.29 (1.19, 1.39)	−0.236	−0.378, −0.094	.001
		6	1.04 (0.94, 1.13)	1.21 (1.12, 1.30)	−0.174	−0.309, −0.038	.012
Asthma symptom days (% days)	Maintenance ICS-formoterol	1	39.56 (37.24, 41.89)	40.45 (38.19, 42.70)	−0.885	−4.126, 2.356	.593
		3	37.22 (34.85, 39.59)	40.91 (38.61, 43.21)	−3.688	−6.985, −0.390	.028
		6	36.97 (34.57, 39.37)	39.92 (37.59, 42.26)	−2.953	−6.302, 0.397	.084
Use of study reliever medication (doses/d)	Maintenance ICS-salmeterol	1	1.42 (1.33, 1.51)	1.45 (1.37, 1.53)	−0.029	−0.148, 0.091	.640
		3	1.40 (1.32, 1.49)	1.45 (1.37, 1.54)	−0.051	−0.172, 0.069	.403
		6	1.38 (1.29, 1.46)	1.45 (1.36, 1.53)	−0.071	−0.194, 0.052	.258
Asthma symptom days (% days)	Maintenance ICS-salmeterol	1	44.84 (42.95, 46.73)	43.64 (41.80, 45.47)	1.201	−1.432, 3.833	.371
		3	44.73 (42.80, 46.66)	42.99 (41.12, 44.86)	1.743	−0.944, 4.429	.204
		6	43.33 (41.37, 45.29)	42.21 (40.30, 44.11)	1.121	−1.613, 3.856	.422

Statistical analysis used a mixed-effects model with treatment and treatment*period interaction as fixed effects. Patient was included as a random effect. The variance-covariance matrix was assumed to be unstructured.

Eighteen countries used salbutamol via pressurized metered-dose inhaler (200 µg per dose), 1 via Diskhaler (200 µg per dose), 2 via Diskus (200 µg per dose), and 3 via Turbuhaler (100 µg per dose). Patients were advised to take 1 inhalation as needed, regardless of the device. *CI*, confidence interval; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *LS*, least squares; *mo*, month.

sensitive and regulatory kinases and on channels that have been related to disease severity, but it was not possible to test this in the present study.

Although the RELIEF study is strengthened by its large sample size, the study has some limitations that are inherent to *post hoc* analyses and to the nature of the RELIEF trial. *Post hoc* analyses do not always conform to the original study aims and analyses, and neither the subgroups used in this study nor the randomization model of statistical inference was prespecified, leading to a potential bias toward positive results. Being an open-label study comparing a new medication with a familiar and widely used medication, the safety outcomes, especially those assessing discontinuation of treatment, may also be biased. The original study used the then-current guideline definition of severe exacerbations, including a course of oral corticosteroids lasting ≥ 5 days, which has since changed to ≥ 3 days after the recommendations of an American Thoracic Society/European Respiratory Society Task Force.¹⁶ The present analysis found little evidence of greater effectiveness of as-needed formoterol compared with as-needed salbutamol in patients on maintenance ICS-salmeterol. However, the as-needed combination ICS-formoterol could still potentially be more effective than as-needed SABA in patients on maintenance ICS-salmeterol. Indeed, the RELIEF study did not evaluate the ICS component of the combination reliever currently recommended by GINA⁹ and the NAEPP focused update.¹¹ The study was also limited by the fact that salmeterol was the only nonformoterol LABA considered. LABA greatly differ in their efficiency of muscle relaxation, ability to induce bronchoprotection (ie, protection against a contractile substance or stimulus), and their mechanism of downregulation or tolerance. It is therefore difficult to generalize the findings of this *post hoc* analysis to

LABAs in general. However, it may be speculated that, due to similarities in their pharmacology, maintenance ICS-indacaterol could potentially have results in line with those observed with maintenance ICS-formoterol, whereas ICS-vilanterol is more likely to behave similarly to ICS-salmeterol. Further research into the pharmacology of these drugs and how they interact with other treatments is needed.

CONCLUSIONS

In this *post hoc* analysis of the RELIEF study, there was no evidence of increased risk of SAEs and/or DAEs with as-needed formoterol versus as-needed salbutamol, regardless of type of ICS-LABA maintenance therapy at study entry. However, in patients taking maintenance ICS-salmeterol, the use of as-needed formoterol versus as-needed salbutamol was associated with more DAEs, specifically nonserious and non-asthma-related DAEs, than in patients taking maintenance ICS-formoterol. There was also little evidence of reduced exacerbations with as-needed formoterol compared with as-needed salbutamol in patients taking maintenance ICS-salmeterol, unlike the well-known reduction in severe exacerbations with as-needed ICS-formoterol used either alone or with maintenance ICS-formoterol (MART). At the time these analyses were performed, as-needed SABA was the only recommended reliever option for asthma patients taking maintenance non-formoterol ICS-LABAs. However, the recently published GINA 2023 Strategy Report included as-needed combination ICS-SABA as an alternative reliever option for adults and adolescents in Track 2 Steps 3–5,⁹ based on the reduction in risk of severe exacerbations with ICS-SABA reliever compared with SABA reliever in the MANDALA study.³³ The present

findings do not provide sufficient evidence to support use of ICS-formoterol as reliever in patients taking maintenance non-formoterol ICS-LABA, at least for maintenance ICS-salmeterol; prospective safety and effectiveness studies would be needed. For such patients, the best option at present may be to use a combination ICS-SABA reliever, if available, as this would reduce the risk of severe exacerbations compared with using a SABA-only reliever.

Acknowledgments

The authors acknowledge Tore Persson of NMSP Statistikprogram, Nick Sanders of AstraZeneca, and Annika Syrnén of I-Mind Consulting, who provided statistical analysis. The authors would like to thank Marco Emanuele Favretto (PhD, MSc, PGCHE) of inScience Communications, Springer Healthcare Ltd, UK, for providing medical writing support in accordance with Good Publication Practice (GPP) 2022 guidelines³⁴ and funded by AstraZeneca.

H. K. Reddel, G. Brusselle, and G. P. Anderson contributed to the study concept and design, data interpretation, and writing, review, and final approval of the manuscript. R. Lamarca, P. Gustafson, and C. Jorup contributed to data preparation, statistical analysis, data interpretation, and review and final approval of the manuscript.

REFERENCES

- Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting β -agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018;319:1485-96.
- Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013;(4):CD007313.
- Demoly P, Louis R, Spies-Petersen U, Naya I, Carlsheimer A, Worth H, et al. Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med* 2009;103:1623-32.
- Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019;380:2020-30.
- O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
- Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87.
- Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRAC-TICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019;394:919-28.
- Crossingham I, Turner S, Ramakrishnan S, Fries A, Gowell M, Yasmin F, et al. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. *Cochrane Database Syst Rev* 2021;5:CD013518.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2023. Accessed May 4, 2023. <https://ginasthma.org/2023-gina-main-report/>
- Reddel HK, Bateman ED, Schatz M, Krishnan JA, Cloutier MM. A practical guide to implementing SMART in asthma management. *J Allergy Clin Immunol Pract* 2022;10:S31-8.
- National Asthma Education and Prevention Program. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Accessed May 5, 2023. <https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines>
- Pauwels RA, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003;22:787-94.
- Chapman KR, Friberg K, Balter MS, Hyland RH, Alexander M, Abboud RT, et al. Albuterol via Turbuhaler versus albuterol via pressurized metered-dose inhaler in asthma. *Ann Allergy Asthma Immunol* 1997;78:59-63.
- Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
- Guhan AR, Cooper S, Osborne J, Lewis S, Bennett J, Tattersfield AE. Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects. *Thorax* 2000;55:650-6.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
- Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. *J Allergy Clin Immunol Pract* 2022;10:S1-18.
- Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemost* 2011;9:2153-8.
- Jones WS, Mulder H, Wruck LM, Pencina MJ, Kripalani S, Munoz D, et al. Comparative effectiveness of aspirin dosing in cardiovascular disease. *N Engl J Med* 2021;384:1981-90.
- Anderson GP, Lindén A, Rabe KF. Why are long-acting beta-adrenoceptor agonists long-acting? *Eur Respir J* 1994;7:569-78.
- Naline E, Zhang Y, Qian Y, Mairon N, Anderson GP, Grandordy B, et al. Relaxant effects and durations of action of formoterol and salmeterol on the isolated human bronchus. *Eur Respir J* 1994;7:914-20.
- Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med* 1999;160:244-9.
- Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.
- Molimard M, Naline E, Zhang Y, Le Gros V, Begaud B, Advenier C. Long- and short-acting beta2 adrenoceptor agonists: interactions in human contracted bronchi. *Eur Respir J* 1998;11:583-8.
- Korosec M, Novak RD, Myers E, Skowronski M, McFadden ER Jr. Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999;107:209-13.
- Giembycz MA. An estimation of beta 2-adrenoceptor reserve on human bronchial smooth muscle for some sympathomimetic bronchodilators. *Br J Pharmacol* 2009;158:287-99.
- Anderson GP. Long acting inhaled beta-adrenoceptor agonists the comparative pharmacology of formoterol and salmeterol. *Agents Actions Suppl* 1993;43:253-69.
- Lötvall J. Pharmacological similarities and differences between beta2-agonists. *Respir Med* 2001;95(Suppl B):S7-11.
- Hancox RJ. Interactions between corticosteroids and beta2-agonists. *Clin Rev Allergy Immunol* 2006;31:231-46.
- Lipworth BJ, Hall IP, Aziz I, Tan KS, Wheatley A. Beta2-adrenoceptor polymorphism and bronchoprotective sensitivity with regular short- and long-acting beta2-agonist therapy. *Clin Sci (Lond)* 1999;96:253-9.
- Wechsler ME, Lehman E, Lazarus SC, Lemanske RF Jr, Boushey HA, Deykin A, et al. β -Adrenergic receptor polymorphisms and response to salmeterol. *Am J Respir Crit Care Med* 2006;173:519-26.
- Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364:1505-12.
- Papi A, Chipps BE, Beasley R, Panettieri RA Jr, Israel E, Cooper M, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med* 2022;386:2071-83.
- DeTora LM, Lane T, Sykes A, DiBiasi F, Toroser D, Citrome L. Update. *Ann Intern Med* 2022;176(2023):eL220490.

ONLINE REPOSITORY

LITERATURE SEARCH

A literature search was undertaken on PubMed to identify any randomized controlled trials in patients receiving maintenance nonformoterol long-acting β_2 -agonist (LABA)/inhaled corticosteroid (ICS)-containing medications who had been treated with as-needed formoterol or as-needed ICS-formoterol as reliever, published between 1997 and 2022.

Search string

(asthma AND formoterol AND salmeterol AND reliever) OR (asthma AND formoterol AND salmeterol AND rescue) OR (asthma AND formoterol AND salmeterol AND as-needed) OR (asthma AND formoterol AND salmeterol AND prn) OR (asthma AND formoterol AND vilanterol AND reliever) OR (asthma AND formoterol AND vilanterol AND rescue) OR (asthma AND formoterol AND vilanterol AND as-needed) OR (asthma AND formoterol AND Vilanterol AND prn) OR (asthma AND formoterol AND indicaterol AND reliever) OR (asthma AND formoterol AND indicaterol AND rescue) OR (asthma AND formoterol AND indicaterol AND as-needed) OR (asthma AND formoterol AND indicaterol AND prn) OR (asthma AND (as-needed formoterol) AND (formoterol maintenance)) OR ((asthma AND (formoterol rescue) AND (formoterol maintenance)) OR (asthma AND (formoterol reliever) AND (formoterol maintenance)) OR (asthma AND (rescue formoterol) AND (formoterol maintenance)) OR ((asthma AND (formoterol rescue) AND (formoterol maintenance)) OR (asthma AND (formoterol reliever) AND (formoterol maintenance)) OR (asthma AND (as-needed formoterol) AND (formoterol controller)) OR ((asthma AND (formoterol as-needed) AND (formoterol controller)) OR (asthma AND (formoterol reliever) AND (formoterol controller)) AND (safety)

PubMed filters: "clinical trial" and "randomized clinical trial"

The above search yielded a total of 105 studies, of which 67 were excluded as they were observational or non-randomized studies, or describing a protocol/study design; 1 randomized controlled trial was excluded as it was investigating patients with chronic obstructive pulmonary disease, and 1 randomized controlled study was excluded as it was a duplicate entry. Of the 37 randomized controlled trials in asthma, 17 studies were excluded because they did not include use of as-needed formoterol or ICS-formoterol. Two studies that potentially included some patients taking as-needed formoterol were excluded from analysis because no safety or efficacy data were reported for this subset of patients. A further 17 studies were excluded because they did not include a maintenance non-formoterol LABA (with or without maintenance ICS). The remaining 2 studies were the RELIEF study^{E24} and a subgroup analysis of patients in the RELIEF study in East Asia.^{E7}

RESULTS

Safety—deaths

In the RELIEF study, there was 1 death (0.1%) each with as-needed formoterol and as-needed salbutamol (both caused by myocardial infarction) in patients receiving ICS-formoterol maintenance therapy at study entry. In patients receiving ICS-salmeterol maintenance at study entry, 2 deaths (0.1%) were reported with as-needed salbutamol (both myocardial infarction) and 4 deaths (0.3%) with as-needed formoterol; 3 were cardiac related, and 1 was caused by severe asthma exacerbation. The latter patient was randomized into the study on the day before the death. The only dose of the investigational product was taken approximately 7 hours before the event. The patient was pronounced dead on arrival at hospital. The probable cause of death was acute bronchial asthma. The investigator considered the causal relationship as unlikely.

TABLE E1. Baseline characteristic of patients by medication use

Background treatment	Maintenance ICS-formoterol bid			Maintenance ICS-salmeterol bid		
	As-needed formoterol (n = 1044)	As-needed salbutamol (n = 1098)	P value	As-needed formoterol (n = 1605)	As-needed salbutamol (n = 1689)	P value
Age, mean (SD) (y)	44.4 (17.4)	43.8 (17.4)	.4422	43.8 (18.4)	43.4 (18.2)	.5189
Children (%)	2.7	2.6	.6187	3.9	3.7	.9787
Adolescents (%)	3.8	4.8		6.9	7.0	
Adults (%)	79.7	80.0		75.0	75.4	
Elderly (%)	13.8	12.7		14.2	13.9	
Female (%)	59.3	64.2	.0192	59.9	59.7	.9077
Race (%)			.1269			.4088
White [†]	96.7	97.8		94.5	93.8	
Black, Asian [‡] , or other	3.3	2.2		5.5	6.2	
Regular smoker (%)	14.6	15.4	.5896	15.7	15.2	.7004
Regular exercise (%)	41.9	39.6	.2914	43.0	41.1	.2844
Asthma medication level* (%)			.9912			.4856
Mild	22.1	22.2		17.1	18.7	
Moderate	46.6	46.7		40.1	39.0	
Severe	31.3	31.1		42.8	42.3	
Educational level (%)			.0631			.9646
<10 y	31.2	31.4		30.0	30.0	
≥10 but <14 y	38.7	42.7		40.9	41.3	
≥14 y	30.1	25.9		29.1	28.7	
Employment status (%)			.7797			.2622
Unemployed	30.9	30.0		33.0	30.7	
Employed	52.4	53.9		50.5	53.2	
House person	16.7	16.1		16.5	16.0	

bid, Twice daily; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *LM*, leukotriene modifier; *LTRA*, leukotriene receptor antagonists; *SABA*, short-acting β_2 -agonists; *SCS*, systemic corticosteroids; *SD*, standard deviation.

*Classification as in the original RELIEF study based on maintenance treatment. Mild: use of ICS at a daily dose of <500 μ g or use of LABA, cromoglycate, nedocromil, theophylline, LM, or other asthma medication including SABA, antihistamines, and anticholinergics. Moderate: use of ICS at a daily dose of $\geq$ 500 μ g, or a daily dose of 500 to 800 μ g and LABA/theophylline or LM. Severe: use of ICS at a daily dose of >800 μ g and use of LABA, theophylline, LTRA, or SCS. [†]Term used in original study was caucasian. [‡]Term used in original study was oriental.

REFERENCES

- E1. Bateman ED, Bantje TA, João Gomes M, Toubis MG, Huber RM, Naya I, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. *Am J Respir Med* 2003;2:275-81.
- E2. Bateman ED, O'Byrne PM, FitzGerald JM, Barnes PJ, Zheng J, Lamarca R, et al. Positioning as-needed budesonide-formoterol for mild asthma: effect of prestudy treatment in pooled analysis of SYGMA 1 and 2. *Ann Am Thorac Soc* 2021;18:2007-17.
- E3. Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. *Allergy Asthma Proc* 2010;31:49-59.
- E4. Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulm Med* 2011;11:28.
- E5. Bouros D, Bachlitzanakis N, Kottakis J, Pfister P, Polychronopoulos V, Papadakis E, et al. Formoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. *Eur Respir J* 1999;14:627-32.
- E6. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, et al. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. *Respir Res* 2012;13:59.
- E7. Cheng QJ, Huang SG, Chen YZ, Lin JT, Zhou X, Chen BY, et al. Formoterol as reliever medication in asthma: a post-hoc analysis of the subgroup of the RELIEF study in East Asia. *BMC Pulm Med* 2016;16:8.
- E8. Condemni JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open-label trial. *Clin Ther* 2001;23:1529-41.
- E9. Eid NS, Noonan MJ, Chippis B, Parasuraman B, Miller CJ, O'Brien CD. Once- vs twice-daily budesonide/formoterol in 6- to 15-year-old patients with stable asthma. *Pediatrics* 2010;126:e565-75.
- E10. Emeryk A, Klink R, McIver T, Dalvi P. A 12-week open-label, randomized, controlled trial and 24-week extension to assess the efficacy and safety of fluticasone propionate/formoterol in children with asthma. *Ther Adv Respir Dis* 2016;10:324-37.
- E11. Foster J, Beasley R, Braithwaite I, Harrison T, Holliday M, Pavord I, et al. Perspectives of mild asthma patients on maintenance versus as-needed preventer treatment regimens: a qualitative study. *BMJ Open* 2022;12:e048537.
- E12. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRAC-TICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019;394:919-28.
- E13. Ige OM, Ohaju-Obodo JO, Chukwu C, Peters EJ, Okpapi J, Chukwuka C. Effectiveness and safety of adjustable maintenance dosing with budesonide/formoterol Turbuhaler compared with traditional fixed doses in bronchial asthma: a multi-centre Nigerian study. *Afr J Med Med Sci* 2010;39:165-72.
- E14. Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J* 2018;51:1701688.
- E15. Kanniss F, Scuri M, Vezzoli S, Francisco C, Petruzzelli S. Extrafine beclomethasone/formoterol combination via a dry powder inhaler (NEXThaler®) or pMDI and beclomethasone monotherapy for maintenance of asthma control in adult patients: a randomised, double-blind trial. *Pulm Pharmacol Ther* 2015;30:121-7.
- E16. Laloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest* 2003;123:1480-7.
- E17. Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. *Int J Clin Pract* 2009;63:1479-88.
- E18. Maspero JF, Nolte H, Chérrez-Ojeda I. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. *J Asthma* 2010;47:1106-15.
- E19. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
- E20. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
- E21. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, et al. Beclomethasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;1:23-31.
- E22. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013;1:32-42.
- E23. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A, Helm C, et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin Exp Allergy* 2013;43:1144-51.
- E24. Pauwels RA, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003;22:787-94.
- E25. Pilcher J, Patel M, Reddel HK, Pritchard A, Black P, Shaw D, et al. Effect of smoking status on the efficacy of the SMART regimen in high risk asthma. *Respirology* 2016;21:858-66.
- E26. Quirce S, Barcina C, Plaza V, Calvo E, Muñoz M, Ampudia R, et al. A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain. *J Asthma* 2011;48:839-47.
- E27. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Laloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
- E28. Reddel HK, O'Byrne PM, FitzGerald JM, Barnes PJ, Zheng J, Ivanov S, et al. Efficacy and safety of as-needed budesonide-formoterol in adolescents with mild asthma. *J Allergy Clin Immunol Pract* 2021;9:3069-3077. e6.
- E29. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. *Respir Med* 2002;96:851-61.
- E30. Saito T, Hasunuma T. Safety and tolerability of high-dose budesonide/formoterol via Turbuhaler® in Japanese patients with asthma: a randomized, double-blind, crossover, active comparator-controlled, phase III study. *Clin Drug Investig* 2012;32:51-61.
- E31. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquet L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004;20:1403-18.
- E32. Sears MR, Boulet LP, Laviolette M, FitzGerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. *Eur Respir J* 2008;31:982-9.
- E33. Tattersfield AE, Löfdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.
- E34. van der Molen T, Postma DS, Turner MO, Jong BM, Malo JL, Chapman K, et al. Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. The Netherlands and Canadian Formoterol Study Investigators. *Thorax* 1997;52:535-9.
- E35. Vervloet D, Ekström T, Pela R, Duce Gracia F, Kopp C, Silvert BD, et al. A 6-month comparison between formoterol and salmeterol in patients with reversible obstructive airways disease. *Respir Med* 1998;92:836-42.
- E36. Wechsler ME, Yawn BP, Fuhlbrigge AL, Pace WD, Pencina MJ, Doros G, et al. Anticholinergic vs long-acting β -agonist in combination with inhaled corticosteroids in black adults with Asthma: the BELT randomized clinical trial. *JAMA* 2015;314:1720-30.
- E37. Zimmerman B, D'Urzo A, Bérubé D. Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. *Pediatr Pulmonol* 2004;37:122-7.