



Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

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Summary

Background In adults with mild asthma, a combination of an inhaled corticosteroid with a fast-onset long-acting β -agonist (LABA) used as reliever monotherapy reduces severe exacerbations compared with short-acting β -agonist (SABA) reliever therapy. We investigated the efficacy of combination budesonide–formoterol reliever therapy compared with maintenance budesonide plus as-needed terbutaline.

Methods We did a 52-week, open-label, parallel-group, multicentre, superiority, randomised controlled trial at 15 primary care or hospital-based clinical trials units and primary care practices in New Zealand. Participants were adults aged 18–75 years with a self-reported doctor's diagnosis of asthma who were using SABA for symptom relief with or without maintenance low to moderate doses of inhaled corticosteroids in the previous 12 weeks. We randomly assigned participants (1:1) to either reliever therapy with budesonide 200 μ g–formoterol 6 μ g Turbuhaler (one inhalation as needed for relief of symptoms) or maintenance budesonide 200 μ g Turbuhaler (one inhalation twice daily) plus terbutaline 250 μ g Turbuhaler (two inhalations as needed). Participants and investigators were not masked to group assignment; the statistician was masked for analysis of the primary outcome. Six study visits were scheduled: randomisation, and weeks 4, 16, 28, 40, and 52. The primary outcome was the number of severe exacerbations per patient per year analysed by intention to treat (severe exacerbations defined as use of systemic corticosteroids for at least 3 days because of asthma, or admission to hospital or an emergency department visit because of asthma requiring systemic corticosteroids). Safety analyses included all participants who had received at least one dose of study treatment. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12616000377437.

Findings Between May 4, 2016, and Dec 22, 2017, we assigned 890 participants to treatment and included 885 eligible participants in the analysis: 437 assigned to budesonide–formoterol as needed and 448 to budesonide maintenance plus terbutaline as needed. Severe exacerbations per patient per year were lower with as-needed budesonide–formoterol than with maintenance budesonide plus terbutaline as needed (absolute rate per patient per year 0.119 vs 0.172; relative rate 0.69, 95% CI 0.48–1.00; $p=0.049$). Nasopharyngitis was the most common adverse event in both groups, occurring in 154 (35%) of 440 patients receiving as-needed budesonide–formoterol and 144 (32%) of 448 receiving maintenance budesonide plus terbutaline as needed.

Interpretation In adults with mild to moderate asthma, budesonide–formoterol used as needed for symptom relief was more effective at preventing severe exacerbations than maintenance low-dose budesonide plus as-needed terbutaline. The findings support the 2019 Global Initiative for Asthma recommendation that inhaled corticosteroid–formoterol reliever therapy is an alternative regimen to daily low-dose inhaled corticosteroid for patients with mild asthma.

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Introduction

Most people with asthma have intermittent or mild disease. Despite generally having few symptoms, these patients still have exacerbations.^{1,2} Many of these exacerbations could be prevented by low-dose inhaled corticosteroids,^{2,3} but health-care professionals often do not prescribe these drugs to patients with intermittent or mild disease and such patients may be poorly adherent, as

the intermittent nature of symptoms makes commitment to a regular maintenance regimen problematic.^{4–6}

An alternative approach is to use a combination of an inhaled corticosteroid with formoterol (a fast-onset long-acting β -agonist [LABA]) as reliever monotherapy, which reduces the risk of severe exacerbations by more than half compared with a short-acting β -agonist (SABA) reliever alone.^{7,8} However there is

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See Online for appendix

Research in context

Evidence before this study

Inhaled corticosteroids taken regularly reduce exacerbation risk in patients with mild asthma; however, in clinical practice adherence to inhaled corticosteroids is poor and the burden of disease from exacerbations is substantive. An alternative approach that potentially overcomes the problem of poor adherence is the use of an inhaled corticosteroid–formoterol combination as sole reliever therapy, thereby titrating use according to symptoms. We searched MEDLINE and Embase for studies published between Jan 1, 2000, and July 1, 2019, using the terms “inhaled corticosteroid–formoterol”, “budesonide–formoterol”, “as-required”, “asthma”, “adults”, and “randomised controlled trial”. Four studies of adults with mild or moderate asthma were identified which investigated the efficacy of budesonide–formoterol reliever monotherapy, all of which were published after this study was designed. In two studies, comparisons were made versus short-acting β -agonist (SABA) reliever monotherapy or with maintenance budesonide plus SABA reliever therapy; in one, versus maintenance budesonide plus SABA reliever therapy; and in one versus regular budesonide–formoterol plus SABA reliever therapy. Budesonide–formoterol reliever therapy was superior to SABA reliever therapy in patients with mild asthma, reducing the risk of severe exacerbations by at least 50% after a follow-up of 12 months. Of the three studies investigating budesonide–formoterol reliever therapy and maintenance budesonide plus SABA reliever therapy in patients with mild asthma, two were regulatory and one was a real-world study; there was non-inferiority in severe exacerbation risk in the two regulatory studies, whereas the real world study reported a significantly lower severe exacerbation risk with budesonide–formoterol reliever therapy compared with maintenance budesonide therapy plus SABA reliever. Budesonide–formoterol reliever monotherapy was inferior to regular budesonide–formoterol plus as-needed SABA for the outcome of treatment failure but not different for severe exacerbations in patients with moderate asthma. As a result, there is uncertainty about the relative efficacy and safety of inhaled corticosteroid–formoterol reliever monotherapy

compared with maintenance inhaled corticosteroid plus SABA reliever therapy.

Added value of this study

This was the first independently funded open-label study comparing inhaled corticosteroid–formoterol reliever therapy with maintenance inhaled corticosteroid plus SABA reliever therapy in adults with mild to moderate asthma in a real-world setting. Budesonide–formoterol reliever therapy resulted in fewer severe exacerbations, and patients on this therapy had a longer time to first severe exacerbation, compared with patients on maintenance budesonide plus as-needed terbutaline. FENO was lower with budesonide maintenance. There was no significant between-group difference in asthma symptom control as measured by Asthma Control Questionnaire 5. The findings of sub-group analyses were consistent with the treatment effect being similar in all patient subgroups, suggesting that the findings are generalisable across the spectrum of mild and moderate asthma.

Implications of all the available evidence

Budesonide–formoterol reliever therapy is superior to maintenance budesonide plus SABA reliever therapy in adults with mild to moderate asthma in the real-world setting, reducing the risk of severe exacerbations without a clinically important worsening in asthma symptom control. Together the available evidence suggests that, for prevention of severe exacerbations, budesonide–formoterol reliever therapy is preferred to SABA reliever therapy for step 1 treatment, confirming the recommendation in the Global Initiative for Asthma (GINA) 2019 guidelines that adults and adolescents with asthma should not be treated with SABA alone. The evidence also supports the inclusion of budesonide–formoterol reliever therapy as an alternative to maintenance low-dose corticosteroids plus SABA reliever in GINA step 2. With the addition of this study, the evidence now also suggests that, of these two regimens, budesonide–formoterol reliever therapy might be the preferred option for prevention of severe exacerbations in mild to moderate asthma.

uncertainty about the relative efficacy and safety of this regimen compared with maintenance inhaled corticosteroid plus as-needed SABA. Two large, randomised, placebo-controlled trials^{7,9} reported non-inferiority in the risk of severe exacerbations between these two regimens, whereas an open-label study more closely aligned to clinical practice reported a halving of the risk of severe exacerbations with budesonide–formoterol reliever therapy compared with maintenance budesonide plus as-needed salbutamol.⁸ In all three studies, maintenance budesonide plus as-needed SABA achieved greater improvement in symptom control, although this improvement was less than the minimum clinically important difference.

We designed the PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist (PRACTICAL) study with the aim of comparing the efficacy of as needed budesonide–formoterol reliever therapy with maintenance budesonide plus as-needed terbutaline in an open-label clinical trial in adults with mild to moderate asthma. This is the first independently funded randomised controlled trial comparing inhaled corticosteroid–formoterol as sole reliever therapy with maintenance inhaled corticosteroid plus SABA reliever therapy in patients with asthma for whom low dose maintenance inhaled corticosteroid therapy was recommended at step 2 of the 2014 Global Initiative for Asthma (GINA) strategy.¹⁰

Methods

Study design and participants

PRACTICAL was an investigator-led, pragmatic, 52 week, open-label, parallel-group, multicentre, superiority, randomised controlled trial undertaken at 15 primary care or hospital-based clinical trials units and primary care practices across New Zealand. Ethical approval was provided by the Northern B Health and Disability Ethics Committee. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and the trial protocol has been published.¹¹

Eligible participants were adults aged 18 to 75 with a self-reported doctor's diagnosis of asthma who were either taking SABA reliever therapy alone or SABA reliever together with low to moderate doses of inhaled corticosteroids in the 12 weeks before randomisation. The main inclusion criteria were 1) for those who had not used an inhaled corticosteroid in the past 12 weeks, the presence of asthma symptoms or need for a SABA on at least two occasions in the past 4 weeks, or waking because of asthma at least once in the past 4 weeks, or a history of a severe asthma exacerbation requiring oral corticosteroids in the past 52 weeks, and 2) for those who had used an inhaled corticosteroid in the previous 12 weeks at low or moderate doses (≤ 800 $\mu\text{g/day}$ budesonide equivalent), partly or well controlled asthma as defined by GINA 2014,¹⁰ or uncontrolled asthma with poor adherence or unsatisfactory inhaler technique. Exclusion criteria were oral corticosteroid use for asthma in the 6 weeks before randomisation, representing recent unstable asthma; a home supply of oral corticosteroids used as part of an asthma action plan; self-reported use of LABA, leukotriene receptor antagonists, theophylline, anticholinergic drugs, or cromones in the 12 weeks before randomisation; self-reported admission to an intensive care unit for asthma ever; a self-reported diagnosis of chronic obstructive pulmonary disease, bronchiectasis, or interstitial lung disease; self-reported greater than 20 pack-years smoking history, or the onset of respiratory symptoms after the age of 40 in current or ex-smokers with at least 10 pack-years smoking history; pregnancy or planned pregnancy during the study period; unwilling or unable to switch from current asthma treatment regimen; other illnesses that were likely to compromise participant safety or affect the feasibility of results, at the discretion of the investigator. There was no standardised method of pre-screening across sites. All participants provided written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) to either reliever therapy with budesonide–formoterol or maintenance budesonide plus terbutaline as needed. Randomisation was stratified by recruitment site and inhaled corticosteroid use before enrolment, using a computer-generated sequence with a block size of eight per site, generated by the statistician. The allocation sequence was concealed

by the electronic case report form system until after randomisation. Site investigators enrolled participants. Participants and investigators were not masked to group assignment; the statistician was masked for analysis of the primary outcome variable.

Procedures

Participants in the budesonide–formoterol group received budesonide 200 μg –formoterol 6 μg (Symbicort Turbuhaler, AstraZeneca), one inhalation for relief of symptoms as required. Patients in the maintenance budesonide plus terbutaline as needed group received budesonide 200 μg (Pulmicort Turbuhaler, AstraZeneca), one inhalation twice daily plus terbutaline 250 μg (Bricanyl Turbuhaler, AstraZeneca), two inhalations for relief of symptoms as required. Participants were provided with an asthma action plan that included when to seek medical review for worsening asthma and a log for recording urgent medical visits and systemic corticosteroid use (appendix pp 27–30). Electronic inhaler usage monitors (Adherium, Auckland, New Zealand) that recorded the date and time of inhaler actuations¹² were incorporated in all inhalers dispensed to a subgroup of participants at two study sites. Participants were aware that the electronic monitors recorded the date and time of their inhaler use. The data from the electronic monitors were not viewed or analysed during the study and participants were made explicitly aware of this. All participants remained under the care of their usual health-care practitioners throughout the study.

Six study visits were scheduled over 52 weeks at week 0 (randomisation visit), and weeks 4, 16, 28, 40, and 52. Baseline participant characteristics were collected at the randomisation visit. On-treatment forced expiratory volume in one s (FEV_1)¹³ and fractional exhaled nitric oxide (FENO) were measured at weeks 0, 16, and 52. Peripheral blood eosinophils were measured at baseline, as was serum periostin in a subgroup. The five-question version of the Asthma Control Questionnaire (ACQ-5)¹⁴ was completed at every study visit. At all study visits following randomisation participants were asked if they had needed to seek urgent medical care for asthma or used oral corticosteroids for worsening asthma. Participants self-reported all adverse or serious adverse events at their subsequent follow up visits. Inhaler technique was checked at every study visit and participants were reminded of their study asthma plan. The schedule of investigations and assessments is in the protocol.¹¹ Patients were withdrawn in the event of treatment failure, defined as either an increase in asthma treatment for 14 days or more made by a health-care provider because of unstable asthma, or uncontrolled asthma resulting in safety concerns as judged by the investigator.

Outcomes

The primary outcome was the number of severe asthma exacerbations per patient per year. Severe asthma

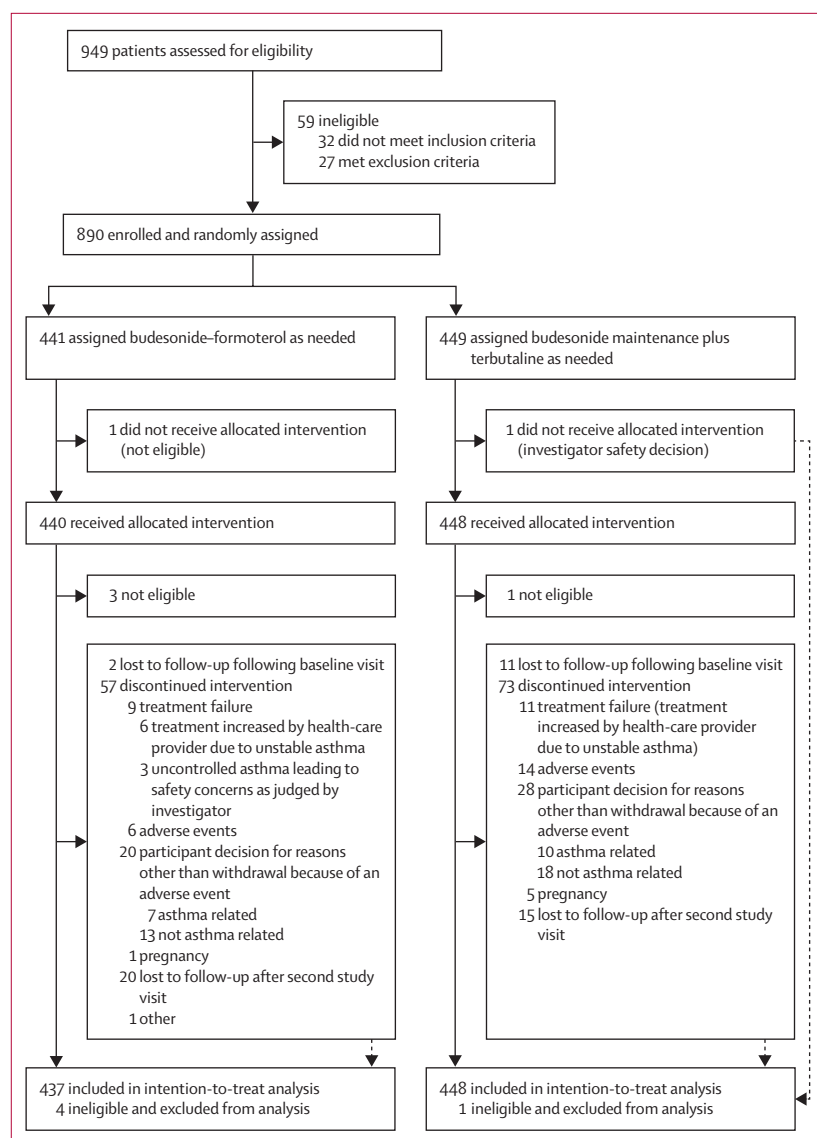


Figure 1: Trial profile

exacerbations were defined by American Thoracic Society/European Respiratory Society (ATS/ERS) criteria:¹³ the use of systemic corticosteroids for at least 3 days because of asthma, or hospital admission or emergency department visit because of asthma, requiring systemic corticosteroids.

Secondary outcomes were the proportion of severe exacerbations defined by the same criteria as for the primary outcome; the proportion of patients with a least one severe exacerbation; time to first severe exacerbation; number of asthma exacerbations per patient per year, including both moderate and severe exacerbations, defined as worsening asthma resulting in unplanned medical review (primary care, visit to emergency department, or hospital admission) or worsening asthma resulting in use of systemic corticosteroids for any

duration; time to first moderate or severe exacerbation; the proportion of patients withdrawn due to treatment failure; proportion of participants prescribed oral corticosteroids for at least three days following urgent medical review; the ACQ-5 score (the mean of five questions about asthma symptoms during the previous week, each scored on a 7-point scale between 0 [no impairment] and 6 [maximum impairment]);¹⁴ on-treatment FEV₁ (L),¹⁵ FENO (parts per billion); adverse events and serious adverse events; and for the electronic monitoring substudy, electronically-recorded budesonide dose per day and electronically-recorded β -agonist actuations per day. Full details of the methods and the statistical analysis plan are in the online protocol¹¹ and appendix (pp 7–11).

Statistical analysis

A sample size of 445 in each treatment arm, which accounted for a 10% dropout rate, had a 90% power and α 5%, to detect a relative rate of severe exacerbations of 0.62, representing a reduction from 0.30 to 0.185 per patient per year. A masked re-estimation of the sample size was done at a planned interim safety analysis after 500 participants had been recruited and randomly assigned to treatment. The overall rate of severe exacerbations at the interim analysis was 0.09 across both arms, lower than the estimated 0.30 per patient per year. The required sample size for the study to be adequately powered to detect the proposed 0.62 relative rate of severe exacerbations would have been 2112 participants. Neither the funding nor the capacity was in place to allow this and therefore the study continued with the original primary outcome variable and planned sample size of 890.

For the electronic monitoring substudy, a sample size of 55 in each treatment arm, which accounted for a 10% dropout rate, had 90% power and α 5% to detect an 18% difference in mean daily budesonide use (μ g/day) with budesonide-formoterol, compared with 264 μ g/day in the maintenance budesonide plus as-needed terbutaline group. This calculation was based on data from our previous study of inhaled corticosteroid adherence in stable asthma in which participants took a mean (SD) 66% (27) of their prescribed inhaled corticosteroid dose.¹⁵

The statistical analysis was an intention-to-treat superiority analysis. The primary analysis was comparison of the number of severe exacerbations per patient per year by Poisson regression with an offset for the time of observation. No adjustment for over-dispersion was used because the degree of freedom was close to the deviance indicating that over-dispersion was unlikely to be a problem. A sensitivity analysis was undertaken to account for different distributions of potential predictors of response, and modelled the following covariates: age, sex, ethnicity, smoking status, baseline ACQ-5, severe exacerbation in previous year (yes/no), baseline inhaled

corticosteroid use, baseline SABA use (in previous 4 weeks), baseline FENO, and baseline blood eosinophil count. Analysis of the combined rate of moderate and severe exacerbations per patient per year was likewise by Poisson regression with an offset for number of days in the study.

Survival analysis with Kaplan-Meier plots and Cox proportional hazards regression was used to calculate the hazard ratio (HR) for the time to first severe exacerbation and first moderate or severe exacerbation. Continuous variables, such as ACQ-5 and FEV₁, were compared by *t* tests and mixed linear models to examine patterns of change with time. For FENO, data were log transformed and differences in logarithms analysed as the ratio of geometric means. Interaction models were used to test for subgroup effects. The Wilcoxon test and the Hodges-Lehmann estimate of location difference were used to compare oral corticosteroid doses between treatment groups. Logistic regression was used to compare the proportion of participants with at least one severe exacerbation, the proportion of participants who withdrew, adverse events, and severe adverse events between the two treatment arms. The safety analysis dataset included all participants who had received at least one dose of randomised treatment. Summary statistics were presented as the number (%) for categorical data and mean (SD) or median (IQR) for continuous data. The primary analysis of the electronic monitoring substudy was comparison of mean budesonide dose per day by *t* test. SAS version 9.4 was used for all analyses. An independent data safety monitoring committee reviewed all serious adverse events. This trial was registered with the Australian and New Zealand Clinical Trials Registry, ACTRN12616000377437.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 4, 2016, and Dec 22, 2017, we assigned 890 participants to treatment (figure 1); the intention-to-treat dataset included 885 eligible participants (baseline characteristics are in table 1, and the appendix pp 31–34). No follow-up data were available for 14 participants (appendix p 35). At study entry participants had a mean ACQ-score of 1.15; 12% reported a severe exacerbation in the previous 12 months. At baseline 264 (30%) of 885 participants were taking SABA reliever therapy alone and 621 (70%) were taking an inhaled corticosteroid. The results of all statistical analyses undertaken are in the appendix (pp 13–25 and 37–62).

The rate of severe asthma exacerbations was lower with as-needed budesonide-formoterol than budesonide

	Budesonide-formoterol as needed (n=437)	Budesonide maintenance plus terbutaline as needed (n=448)
Age (years)	43.3 (15.2)	42.8 (16.7)
BMI (kg/m ²)	29.4 (7.1)	28.0 (5.8)
Sex		
Female	244 (56%)	241 (54%)
Male	193 (44%)	207 (46%)
Ethnic origin		
Asian	29 (7%)	34 (8%)
European	342 (78%)	357 (80%)
Māori	41 (10%)	31 (7%)
Pacific	20 (5%)	16 (4%)
Other	5 (1%)	10 (2%)
Smoking status		
Current	39 (9%)	24 (5%)
Ex-smoker	123 (28%)	112 (25%)
Never	275 (63%)	312 (70%)
Pack-years (among ever smokers)	4.5 (4.7)	4.6 (4.7)
Age at diagnosis (years)	19.5 (17.7)	18.8 (18.1)
Patient-reported use of inhaled corticosteroids in the 12 weeks before enrolment	305 (70%)	316 (71%)
Patient-reported adherence to inhaled corticosteroids in the 4 weeks before enrolment (percentage of prescribed dose)	54.8% (37.0; n=304)	58.6% (47.3; n=315)
Patient-reported use of inhaled corticosteroids ever	390 (89%)	381 (85%)
Patient-reported SABA use in 4 weeks before enrolment (occasions per week)		
Mean (SD)	4.3 (6.0)	4.9 (7.5)
Median (IQR)	2.0 (1.0–5.5)	2.3 (1.0–6.0)
Range	0–70	0–84
Hospital admissions for asthma during lifetime (number per patient)	0.7 (5.1)	0.5 (2.1)
Severe exacerbation in the previous 12 months		
0	384 (88%)	396 (88%)
1	45 (10%)	41 (9%)
2	5 (1%)	7 (2%)
3	3 (<1%)	3 (<1%)
4	0	1 (<1%)
Any	53 (12%)	52 (12%)
ACQ-5 score*	1.1 (0.8)	1.2 (0.8)
GINA symptom control		
Well controlled	101 (23%)	103 (23%)
Partly controlled	209 (48%)	226 (51%)
Uncontrolled	127 (29%)	119 (27%)
On-treatment FEV ₁ (percentage of predicted value†)	87.8% (16.4)	87.4% (16.3)
FENO (parts per billion)	26.0 (15.0–51.0)	30.0 (18.0–62.5)
Blood eosinophil count (×10 ⁹ per L)	0.3 (0.2)	0.3 (0.2)

Data are means (SD) or median (IQR) unless stated otherwise. BMI=body-mass index. SABA=short-acting β_2 -agonist. ACQ-5=Asthma Control Questionnaire-5. GINA=Global Initiative for Asthma. FEV₁=forced expiratory volume in 1 s. FENO=fraction of exhaled nitric oxide. *The ACQ-5 consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment) and averaged; a 0.5-unit change represents the minimal clinically important difference. †Participants received no specific instruction to withhold use of their bronchodilator before measurement of FEV₁.¹³

Table 1: Baseline characteristics of intention-to-treat population

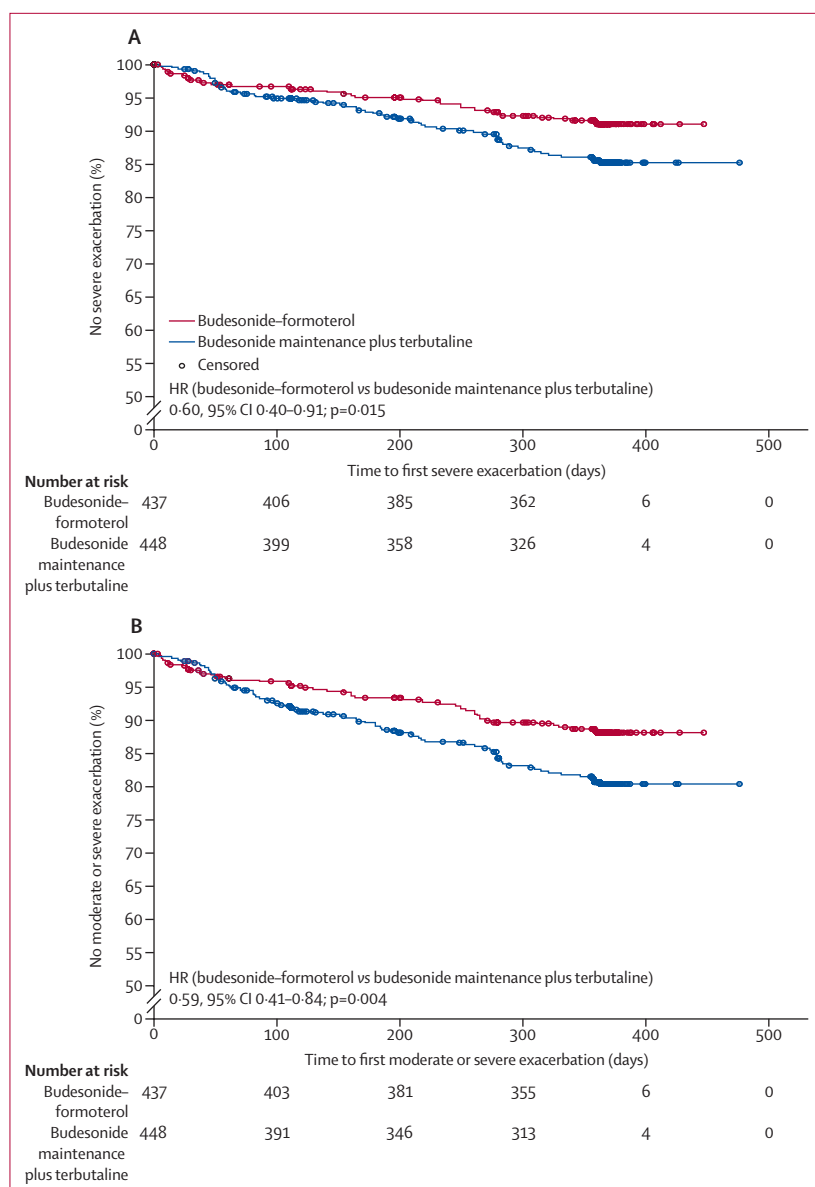


Figure 2: Estimates of the occurrence of exacerbations in a time-to-event analysis

Graphs show (A) time to first severe exacerbation and (B) time to first moderate or severe exacerbation. HR=hazard ratio.

maintenance plus as-needed terbutaline therapy (absolute rate per patient per year 0.119 vs 0.172; relative rate 0.69; 95% CI 0.48–1.00; p=0.049; appendix p 38). In the sensitivity analyses, the relative rates were robust to the included covariates (appendix p 55).

Time to first severe exacerbation was longer with budesonide-formoterol than budesonide maintenance plus as-needed terbutaline (figure 2; appendix p 39). The number of severe exacerbations resulting in an emergency department visit or hospital admission was five and 0, respectively, with as-needed budesonide-formoterol and seven and two, respectively, with budesonide maintenance plus as-needed terbutaline.

The combined moderate and severe asthma exacerbation rate was lower with as-needed budesonide-formoterol than budesonide maintenance plus as-needed terbutaline (absolute rate per patient per year 0.165 vs 0.237; relative rate 0.70; 95% CI 0.51–0.95; p=0.024; appendix p 41). Time to first moderate or severe exacerbation was longer with as-needed budesonide-formoterol than budesonide maintenance (figure 2; appendix p 41). The number of patients who were withdrawn because of treatment failure did not differ between groups (nine in the budesonide-formoterol group vs 11 in the budesonide maintenance plus terbutaline group; relative risk [RR] 0.84, 95% CI 0.35–2.00, p=0.69; appendix p 51).

Across all timepoints, ACQ-5 score with budesonide-formoterol did not differ from budesonide maintenance plus terbutaline (mean difference 0.06, 95% CI –0.005 to 0.12; p=0.07; appendix pp 15, 16, and 45). Additionally across all timepoints, FEV₁ with budesonide-formoterol did not differ from budesonide maintenance plus terbutaline (mean difference 0.006 L; 95% CI –0.026 to 0.04; p=0.69; appendix pp 17, 18, and 46).

FENO was widely skewed at baseline (table 1; appendix p 19). At 12 months, median FENO was 26 parts per billion (IQR 16–45) with budesonide-formoterol and 25 parts per billion (16–40) with budesonide maintenance plus terbutaline (appendix p 46). The geometric mean FENO across all timepoints with budesonide-formoterol was higher than with budesonide maintenance (ratio of geometric means 1.13, 95% CI 1.07–1.21; p<0.001; appendix p 47).

In participants taking SABA monotherapy at baseline, the median FENO was 32.5 parts per billion (IQR 15.0–61.5) at baseline and 24.0 parts per billion (16.0–41.0) at the final study visit in the budesonide-formoterol group versus 45.0 parts per billion (IQR 23.0–91.5) at baseline and 27 parts per billion (16–43) at the final visit in the budesonide maintenance plus terbutaline group (appendix p 48). In participants taking inhaled corticosteroids at baseline, median FENO was 25 parts per billion (IQR 15–48) at baseline and 27 parts per billion (17–46) at final study visit in the budesonide-formoterol group versus 27.5 (IQR 16.5–54.0) at baseline and 24 parts per billion (15–39) at the final visit in the budesonide maintenance group (appendix p 48).

Pre-specified analyses testing the interaction of randomised treatment with various subgroups identified that the highest quartile of baseline blood eosinophils ($\geq 0.4 \times 10^9/L$) was associated with a greater reduction in ACQ-5, but not in severe exacerbations, with budesonide maintenance compared with as-needed budesonide-formoterol. Otherwise there was no evidence of effect modification with respect to severe exacerbations or ACQ-5, based on baseline subgroups of age, sex, ethnicity, smoking status, exacerbation history, inhaled corticosteroid use at baseline, adherence to inhaled

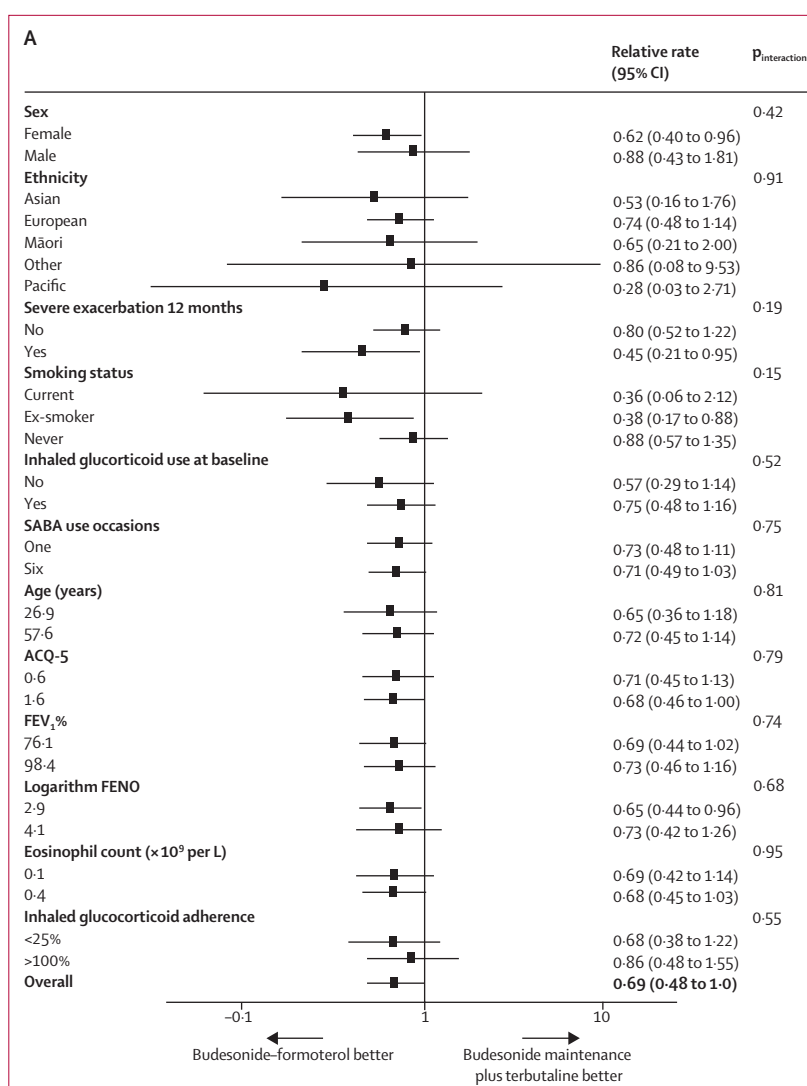
corticosteroid at baseline, baseline SABA use, ACQ-5, percentage of predicted FEV₁, and FENO (figure 3; appendix pp 56–59).

The proportion of participants prescribed oral steroids for at least 3 days following urgent medical review was 52 (78%) of 67 with as-needed budesonide–formoterol and 68 (72%) of 94 with budesonide maintenance plus terbutaline (appendix pp 39 and 42). 110 participants received inhalers containing electronic usage monitors. The characteristics of these 110 participants were similar to those of the full study population (appendix p 36). The mean dose of budesonide was less with budesonide–formoterol than with budesonide maintenance plus terbutaline, (difference -126.5 μg per day; 95% CI -171.0 to -81.9 ; $p < 0.001$; table 2). Overall mean adherence with twice-daily maintenance budesonide in this subgroup was 76%.

Data on all adverse events and serious adverse events are in the appendix (pp 60–62). Nasopharyngitis was the most common adverse event in both groups, occurring in 154 (35%) of 440 patients receiving as-needed budesonide–formoterol and 144 (32%) of 448 receiving maintenance budesonide plus terbutaline (appendix p 61). The number of participants with at least one adverse event was 385 (88%) in the budesonide–formoterol group and 371 (83%) in the budesonide–maintenance plus terbutaline group. There were two hospital admissions due to asthma in the budesonide maintenance group. There were no deaths in the study.

Discussion

This randomised controlled trial provided modest evidence that combination budesonide–formoterol used as-needed for symptom relief reduced the rate of severe exacerbations compared with maintenance low-dose budesonide plus terbutaline as needed in adults with mild to moderate asthma, for whom low-dose inhaled corticosteroids or as-needed inhaled corticosteroids–formoterol are, as of 2019, recommended.¹⁶ The 31% reduction in severe exacerbation risk was achieved despite participants using about 60% of the dose of budesonide and with no difference in symptom control. These findings suggest that titrating the dose of inhaled corticosteroids through as-needed use of a combination inhaler which also delivers a fast-onset LABA is more effective for prevention of severe exacerbations than maintenance inhaled corticosteroids with as-needed SABA in patients with mild to moderate asthma. The timing of inhaled corticosteroid administration is probably a more important determinant of efficacy than the total dose, and a symptom-driven increase in the dose of inhaled corticosteroid in worsening asthma might lead to resolution of an exacerbation before it becomes severe enough for the patient to seek medical review. The co-administration of LABA rather than SABA reliever therapy would also contribute to a reduction in severe exacerbation risk in worsening asthma.¹⁷



(Figure 3 continues on next page)

This study complements the findings of our Novel START study,⁸ which was also undertaken in a real-world setting, enrolled patients with mild asthma taking SABA-only reliever therapy, and in which severe exacerbations was a secondary outcome measure. By contrast, in addition to enrolling patients on a SABA alone, this trial also enrolled those on maintenance low to moderate dose inhaled corticosteroids. In this study, the relative rate of severe exacerbations was 31% lower with as-needed budesonide–formoterol compared with maintenance budesonide plus as-needed terbutaline, whereas in the Novel START study,⁸ the number of severe exacerbations was 56% lower with as-needed budesonide–formoterol than with maintenance budesonide plus as-needed salbutamol. In both this study and Novel START, the 95% CIs were wide with p values close to 0.05, thereby providing modest evidence of superiority, although together providing more certainty

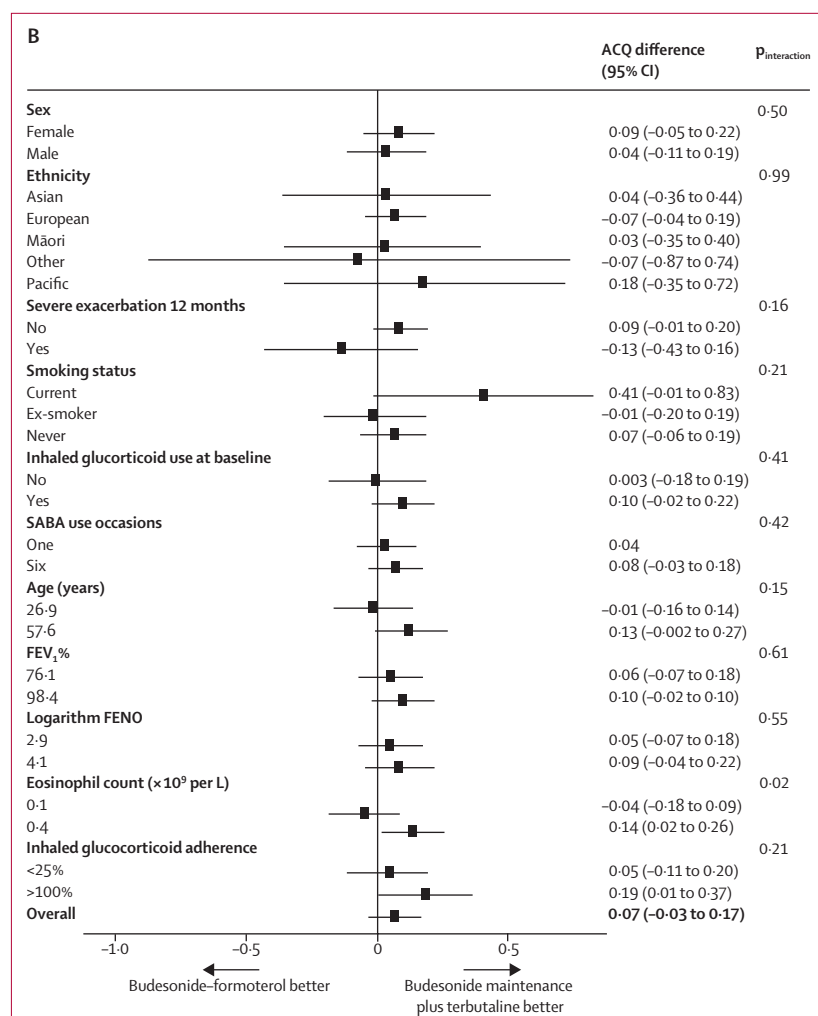


Figure 3: Differential effect of treatment on severe exacerbations and ACQ-5 outcomes

Data shown by potential effect-modifying baseline variables for (A) the relative rate of severe exacerbation and (B) the difference in ACQ-5 score at study end. ACQ-5=Asthma Control Questionnaire-5. SABA=short-acting β -agonist. FEV₁=forced expiratory volume in 1 s. FENO=fraction of exhaled nitric oxide.

about the relative benefit of as-needed inhaled corticosteroids-formoterol in real world settings.

These findings also complement the regulatory SYGMA^{7,9} studies in which there was no significant difference in risk of severe exacerbations between budesonide-formoterol reliever therapy and maintenance budesonide plus SABA reliever, with risk ratios of 0.83 and 0.97. Together, the findings from the four studies suggest that the use of budesonide-formoterol, when taken as sole reliever therapy in a comparatively real-world setting, reduces the risk of severe exacerbations compared with maintenance budesonide plus SABA reliever, whereas this benefit might not be seen in a rigidly-controlled setting with the artificial construct of regular use of a double-dummy placebo inhaler.

Our findings were consistent with those from randomised controlled trials comparing inhaled

	Budesonide-formoterol as needed (n=55)	Budesonide maintenance plus terbutaline as needed (n=55)
Inhaled corticosteroid use		
Number of budesonide-containing actuations per day		
Mean (SD)	0.9 (0.7)	1.5 (0.4)
Median (IQR)	0.8 (0.4-1.3)	1.6 (1.2-1.8)
Range†	0.0-3.4	0.1-2.3
Daily budesonide dose (μ g)		
Mean (SD)	176.0 (143.0)	302.5 (84.8)
Median (IQR)	164.3 (74.0-251.7)	328.3 (245.8-364)
Range‡	6.7-682.5	26.8-458.1
β_2-agonist use		
Number of β_2 -agonist-containing actuations per day		
Mean (SD)	0.9 (0.7)	0.5 (0.6)
Median (IQR)	0.8 (0.4-1.3)	0.3 (0.1-0.6)
Range†	0.0-3.4	0.0-2.7

*Use of inhaled corticosteroids and β_2 -agonists was determined with electronic monitoring of the trial inhalers in a subset of 110 participants. †Range refers to the minimum and maximum mean number of actuations per day. ‡Range refers to the minimum and maximum mean daily dose.

Table 2: Medication outcomes in electronic monitoring subgroups*

corticosteroid-formoterol reliever with SABA reliever in adults with moderate to severe asthma taking maintenance inhaled corticosteroid-LABA therapy. A meta-analysis¹⁸ reported that in adults taking maintenance inhaled corticosteroid-LABA, the use of inhaled corticosteroid-formoterol as the reliever reduced the risk of asthma exacerbations compared with SABA reliever therapy with a relative risk of 0.68 (95% CI 0.58-0.80). This finding suggests that the magnitude of the benefit of inhaled corticosteroid-formoterol reliever therapy compared with SABA reliever therapy is similar across the spectrum of asthma severity, regardless of baseline maintenance therapy.

Our findings also complement the randomised controlled trial which reported that combination beclomethasone-salbutamol reliever therapy had similar efficacy to maintenance beclomethasone plus salbutamol reliever therapy in reducing exacerbation risk and was superior to salbutamol reliever therapy.¹⁹

The findings of the subgroup analyses were consistent with the treatment effect being similar in all participant subgroups, suggesting that the findings are generalisable across the spectrum of mild to moderate asthma. Although the greatest absolute benefit will probably be obtained in those with the greatest morbidity, this finding suggests that clinical profiling is not required for treatment decisions in this population. The only exception to this suggestion might be for patients with high blood eosinophil counts, in whom the highest quartile had a significant reduction in ACQ with maintenance budesonide versus as-needed budesonide-formoterol compared with the lowest quartile, although the difference

of 0·18 was less than the minimum clinically important difference of 0·5,¹⁴ and there was no significant difference in severe exacerbations. For clinical practice, therefore, as part of shared decision making, factors such as patient preference and the likelihood of poor adherence with maintenance inhaled corticosteroid (which would expose the patient to the exacerbation risks of SABA-only treatment) could be considered in making a choice between as-needed budesonide-formoterol and daily maintenance inhaled corticosteroid plus as-needed SABA.

An intrinsic feature of budesonide-formoterol reliever therapy is that if patients are instructed to use this treatment as-needed to relieve symptoms, measures of symptom control would be expected to be worse than with maintenance inhaled corticosteroid treatment. This was noted in three previous studies, which reported higher ACQ scores with as-needed budesonide-formoterol compared with maintenance budesonide, although the differences of 0·11 to 0·15 were short of the minimum clinically important difference of 0·5.⁷⁻⁹ In this study, there was no difference in ACQ-5, with the upper bound of the 95% CI being less than a quarter of the minimum clinically important difference for the ACQ-5 score, and most participants had well controlled asthma (ACQ-5 <1)²⁰ at study end. This finding suggests that, although adequate symptom control is an inherent concern with budesonide-formoterol reliever therapy, it is of doubtful clinical significance. Future studies will need to assess whether budesonide-formoterol reliever therapy taken prophylactically before provoking situations such as exercise, as well as as-needed for symptom relief, results in a greater level of asthma control. In this and the Novel START study, participants were neither encouraged nor discouraged from taking their reliever inhaler prior to exercise.

Consistent with findings from a previous study,⁸ median FENO decreased from 32·5 parts per billion to 24 parts per billion with as-needed budesonide-formoterol in patients who were steroid-naïve at baseline, confirming airways anti-inflammatory effect as measured by FENO. However, overall, maintenance budesonide plus terbutaline had a greater anti-inflammatory effect with a ratio of geometric means of FENO of 1·13, equivalent to a median FENO difference of about 5 parts per billion. The clinical significance of these FENO differences is uncertain because the ATS guidelines propose that a change of at least 20% and 10 parts per billion is required to indicate a clinically significant decrease in FENO following intervention.²¹

Limitations of our study included the open-label design; however, this is the only design that allows the real-world advantage of the inhaled corticosteroid-formoterol reliever regimen, ie, the use of a single inhaler with no maintenance treatment, to be studied. Without a requirement for a twice-daily placebo inhaler, both patient selection and behaviour were likely to be closer to that seen in usual clinical practice (PRECIS-2 wheel, appendix p 26). Study visits (after 1 month and then every 3 months) were

more frequent than usual clinical practice. The study's inclusion criteria ensured that the findings are generalisable to a broad population of adults treated for mild to moderate asthma in the community.^{1,2} Importantly, participants were not required to show bronchodilator reversibility, which has poor sensitivity and specificity for asthma.²² Additionally, current and ex-smokers were included unless they had a greater than 20 pack-year history or for those with a 10 or more pack-year history, the onset of respiratory symptoms after the age of 40 years.

Severe exacerbation rate was the primary outcome variable, as defined and recommended by the ATS/ERS.¹³ Although participants' usual health-care providers were aware of the randomised treatment when consulted during an exacerbation, there was no evidence of systematic bias. In the setting of an unplanned medical review, the probability of a participant being prescribed oral corticosteroids for at least 3 days was similar, regardless of treatment group.

The relative risk for severe exacerbation rate had wide CIs with an upper limit of 1·0. Secondary endpoints were not adjusted for multiplicity of analyses and should not be used to infer definitive treatment effects. The greater number of participants who discontinued intervention in the budesonide maintenance group might have favoured this group, as they might have had more exacerbations following withdrawal, but without having consent for follow-up or recording their treatment after withdrawal, it was not possible to determine the magnitude of any such potential bias.

Electronic monitors were attached to the randomised inhalers for only 110 participants, and as a result measures of inhaled corticosteroid and β -agonist exposure could only be derived from this subgroup. The high adherence rate of 76% in the electronic monitoring sub-group was unexpected and might relate to participants being aware that their devices recorded their inhaler use. However, it also suggests that the comparative benefit of as-needed budesonide-formoterol might have been even greater if adherence was as low as in normal clinical practice.

Our study supports one of the key recommendations of a *Lancet* asthma commission,²³ that in patients with asthma, as-required SABAs should be replaced with combination inhaled corticosteroid-fast-acting β -agonist as reliever therapy for episodic respiratory symptoms regardless of diagnostic label. The findings also provide further evidence in support of the GINA 2019 update, which recommends against SABA-only treatment of adults and adolescents with asthma, and instead recommends inhaled corticosteroid-formoterol reliever therapy for patients with mild asthma. The findings also suggest that, in community patients, as-needed inhaled corticosteroid-formoterol might be preferred over maintenance low-dose inhaled corticosteroid plus as-needed SABA.^{16,24} The next priority will be to investigate the efficacy of as-needed budesonide-formoterol as sole reliever therapy in children, as well as alternative inhaled

corticosteroid–formoterol products and combination inhaled corticosteroid–SABA combinations across the spectrum of asthma severity in children and adults.

In conclusion, budesonide-formoterol reliever therapy was more effective at preventing severe exacerbations than maintenance low-dose twice-daily budesonide plus as-needed terbutaline in adults with mild to moderate asthma, with similar symptom control and a lower dose of inhaled corticosteroid.

Contributors

RB, HKR, RJH, MHa, AC, MWi, PS, JF, and MWe conceived the idea and designed the study. JH, CB, AC, JS, DH, DS, SM, AV, MWi, and JF collected the data. JM and MHo monitored the study. JH, CB, JF, HKR, RJH, JM, MHa, MWi, PS, MHo, MWe, and RB undertook data management and data analysis or data interpretation, or both. All authors had full access to the data analysis report. JH and RB wrote the first draft of the manuscript, and all authors contributed to the final version.

Declaration of interests

JH reports personal fees from AstraZeneca. CB reports personal fees from AstraZeneca and Novartis. AC reports grants from AstraZeneca, resTORbio, Regeneron, Esperion, Connect Biopharma, and Luitpold; and personal fees from AstraZeneca and GlaxoSmithKline. JF reports grants from AstraZeneca, GlaxoSmithKline, and Genentech; and personal fees and non-financial support from AstraZeneca and Boehringer Ingelheim. RJH reports grants from AstraZeneca and Boehringer Ingelheim; and personal fees from Menarini. HKR reports grants from AstraZeneca and Novartis; personal fees from AstraZeneca, GlaxoSmithKline, Merck, Novartis, Teva, Mundipharma, and Boehringer Ingelheim; and is chair of the Global Initiative for Asthma scientific committee. RB reports grants from Genentech, AstraZeneca, GlaxoSmithKline; and personal fees from AstraZeneca and Theravance. All other authors declare no competing interests.

Data sharing

De-identified individual participant data collected during the PRACTICAL trial will be shared at 2 years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to Prof Richard Beasley via email (richard.beasley@mrnz.ac.nz) and will be reviewed by the PRACTICAL study management committee. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

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