Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study

Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study

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Summary

Background Stepwise intensification of inhaled corticosteroids (ICS) is routine for severe eosinophilic asthma, despite some poor responses to high-dose ICS. Dose reductions are recommended in patients responding to biologics, but little supporting safety evidence exists.

Methods SHAMAL was a phase 4, randomised, open-label, active-controlled study done at 22 study sites in four countries. Eligible participants were adults (aged ≥18 years) with severe eosinophilic asthma and a five-item Asthma Control Questionnaire score below 1·5 and who received at least three consecutive doses of benralizumab before screening. We randomly assigned patients (3:1) to taper their high-dose ICS to a medium-dose, low-dose, and as-needed dose (reduction group) or continue (reference group) their ICS–formoterol therapy for 32 weeks, followed by a 16-week maintenance period. The primary endpoint was the proportion of patients reducing their ICS–formoterol dose by week 32. The primary outcome was assessed in the reduction group, and safety analyses included all randomly assigned patients receiving study treatment. This study is registered at ClinicalTrials.gov, NCT04159519.

Findings Between Nov 12, 2019, and Feb 16, 2023, we screened and enrolled in the run-in period 208 patients. We randomly assigned 168 (81%) to the reduction (n=125 [74%]) and reference arms (n=43 [26%]). Overall, 110 (92%) patients reduced their ICS–formoterol dose: 18 (15%) to medium-dose, 20 (17%) to low-dose, and 72 (61%) to as-needed only. In 113 (96%) patients, reductions were maintained to week 48; 114 (91%) of patients in the reduction group had zero exacerbations during tapering. Rates of adverse events were similar between groups. 91 (73%) patients had adverse events in the reduction group and 35 (83%) in the reference group. 17 patients had serious adverse events in the study: 12 (10%) in the reduction group and five (12%) in the reference group. No deaths occurred during the study.

Interpretation These findings show that patients controlled on benralizumab can have meaningful reductions in ICS therapy while maintaining asthma control.

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See Online for appendix

Introduction

Asthma is one of the most common respiratory diseases worldwide, affecting almost 300 million people.[1] Estimates suggest that approximately 3–5% of individuals with asthma have severe disease, characterised by poor symptom control, frequent exacerbations, and high levels of exposure to oral corticosteroids (OCS), which are more damaging than inhaled corticosteroids (ICS). Most of these patients have severe eosinophilic asthma, with uncontrolled eosinophilic and type 2 inflammation, which is of variable steroid responsiveness.[2,3] Interleukin (IL)-5 has been widely linked to eosinophilic inflammation in asthma, with early studies of the IL-5 antagonist mepolizumab showing clinical efficacy in patients with evidence of eosinophilic inflammation.[4] IL-13 induces the eosinophil chemoattractant CCL-26, and IL-13 associated airway inflammation has been linked with airway remodelling.[5] Fractional exhaled nitric oxide (FeNO) is considered the best clinical biomarker of IL-13 pathway activation in asthma.[6]

Benralizumab is an anti-IL-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils through antibody-dependent cell-mediated cytotoxicity.[7] Randomised trials have shown that this mechanistic approach leads to marked reductions in exacerbation rates and OCS exposure, confirming the central, deleterious role of eosinophils in severe eosinophilic asthma. The fact that these patients appeared largely unresponsive to high-dose ICS suggests that lower-dose ICS might be sufficient in

Research in context

Evidence before this study

We searched PubMed on Aug 10, 2023, for previous clinical studies assessing the reduction of high-dose inhaled corticosteroid (ICS) use in patients with severe asthma responding well to biologic treatment. We used the search terms "ICS reduction", "biologic", "benralizumab", "safety", "efficacy", "severe asthma", "severe eosinophilic asthma", and "adverse effects". No language or time restrictions were applied. Articles yielded from this search reported that biologics for the treatment of severe eosinophilic asthma have been shown to reduce asthma exacerbation rates and improve lung function. We also searched PubMed for previous clinical trial reports of "inhaled corticosteroid" "dose reduction" studies in "severe asthma", without time or language restrictions. This search yielded two studies, only one of which assessed a strategy by which to achieve ICS dose reductions. However, the results of that study showed a biomarker-based corticosteroid adjustment strategy was not more effective than the control group approach. Recommendations from the Global Initiative for Asthma suggest reducing ICS doses when possible in patients who respond positively to biologics. However, little clinical evidence exists for best practices regarding safety and extent of ICS dose reductions.

Added value of this study

SHAMAL was a phase 4, multicentre, randomised, open-label, active-controlled, clinical trial that, to our knowledge, was the first to assess ICS reductions while maintaining asthma control in patients with severe eosinophilic asthma that was controlled with benralizumab. Almost all patients were able to reduce their ICS dose while maintaining asthma control and remaining exacerbation free. Patients in the reduction group used less than a third of the total amount of cumulative ICS dose compared with those in the reference group, with no changes in asthma symptom control. Some patients withdrawing from regular ICS had a reduction in lung function, which was weakly correlated with a change in fractional exhaled nitric oxide (FeNO) concentration, suggesting a process mediated by interleukin-13 might underlie lung function decline.

Implications of all the available evidence

These findings highlight the central role of eosinophils in driving exacerbations and poor symptom control in severe eosinophilic asthma. We showed that patients controlled on benralizumab can safely minimise high-dose ICS exposure and their associated adverse effects while maintaining disease control. Our findings underscore the opportunity to shift away from high-dose ICS towards a precision-medicine approach with improved outcomes in patients with severe eosinophilic asthma. Changes in FeNO concentration could further inform reductions in ICS dose by helping to identify patients at the greatest risk of lung function decline.

patients responding well to benralizumab therapy. This question is particularly relevant given the risk of dose-dependent steroid-related morbidity with high-dose ICS (including adrenal suppression, cataracts, fractures, and diabetes)[8,9] and the increased prevalence of clinical remission[2] (sustained absence of significant asthma symptoms by validated instrument, optimisation and stabilisation of lung function, and no use of systemic corticosteroids for exacerbations or disease control for ≥12 months)[10] among patients with severe asthma on biologic therapies.

Global Initiative for Asthma (GINA) recommendations highlight the increased risk of exacerbations associated with short-acting β2-agonist overuse[11–13] and recommend ICS–formoterol as a maintenance and anti-inflammatory reliever treatment (MART) for best outcomes.[3] Compared with short-acting β2-agonist use, anti-inflammatory reliever therapy greatly reduces the risk of severe exacerbations.[3] GINA recommends that doctors reduce ICS doses in patients who respond positively to biologics; however, GINA acknowledges that there is no existing clinical evidence to support the safety or best method for this approach. The SHAMAL study sought to assess the potential for patients with severe eosinophilic asthma responding to benralizumab to reduce their ICS–formoterol maintenance regimen safely and effectively to the smallest dose necessary to maintain asthma control.

Methods

Study design and participants

SHAMAL was a phase 4, multicentre, randomised, open-label, active-controlled study designed to assess whether patients with controlled severe eosinophilic asthma on benralizumab can safely reduce their ICS dose without loss of asthma control. Eligible patients were adults (aged ≥18 years) diagnosed with severe eosinophilic asthma and controlled (five-item Asthma Control Questionnaire [ACQ-5] score <1·5 at visit 1) asthma on high-dose ICS following initiation of benralizumab (≥3 consecutive doses) before visit 1. Key exclusion criteria included history of an exacerbation requiring treatment with systemic corticosteroids within the 3 months before visit 1 or during the run-in period, clinically relevant pulmonary disease other than asthma, and current smoking. Full inclusion and exclusion criteria are provided in the appendix (pp 7–10).

Randomisation criteria included (1) an ACQ-5 of less than 1·5 at visit 2b, (2) no increase (worsening) in ACQ-5 of at least 0·5 units between visits 1 and 2b compared with baseline, (3) zero asthma exacerbations between visits 1 and 2b, and (4) no use of salbutamol for

symptom worsening in more than 3 of the 7 days before visit 2b (unless used for prophylactic reasons—eg, exercise). All participants provided written informed consent.

The study was done at 22 study sites in four countries and consisted of a screening visit (visit 1), a 4–8-week screening and run-in period (for aligning randomisation with the next benralizumab injection), a 32-week reduction period, and a 16-week maintenance period (appendix p 11). The study duration for each patient was approximately 52–56 weeks. Use of other maintenance therapies (such as OCS, leukotriene receptor antagonists, long-acting muscarinic antagonists, or theophyllines) was not allowed during the study, although patients could have been receiving those treatments before study entry and would have undergone different washout periods; any OCS in the 3 months before study entry would have excluded patients from the study.

This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and local regulatory requirements, and adhered to CONSORT guidelines.

Randomisation and masking

During the reduction period, we randomly assigned (3:1) patients to either the treatment-reduction group (benralizumab 30 mg once every 8 weeks plus ICS–formoterol MART starting with medium-dose ICS 200 µg plus formoterol 6 µg for two inhalations twice per day maintenance, plus ICS 200 µg plus formoterol 6 µg as needed, reducing to low-dose ICS–formoterol for one inhalation twice per day maintenance plus ICS–formoterol as needed, and then to ICS–formoterol reliever only) or the reference group (benralizumab 30 mg once every 8 weeks plus high-dose ICS–formoterol maintenance [budesonide 400 µg plus formoterol 12 µg per inhalation]) for two inhalations twice per day and salbutamol reliever as needed.

All patients were centrally assigned to a randomised study treatment using an interactive voice or web response system. Randomisation was stratified by whether the patient consented to participate in a sub-study. Each patient was given the study treatment with the lowest available randomisation number at the site to ensure random allocation.

Patients were assigned unique randomisation numbers sequentially, as patients became eligible. Randomisation numbers were grouped in blocks at an overall level and block sizes were not communicated to investigators. At study completion, randomisation numbers were made available for data analysis. This was an open-label study.

Procedures

The study interventions were (1) benralizumab 30 mg subcutaneous injection once every 8 weeks; (2) high-dose ICS–formoterol (budesonide 400 µg plus formoterol 12 µg per inhalation, two inhalations twice per day); (3) medium-dose ICS–formoterol (budesonide 200 µg plus formoterol 6 µg MART per inhalation, two inhalations twice per day, reliever as needed); (4) low-dose ICS–formoterol (budesonide 200 µg plus formoterol 6 µg MART per inhalation, one inhalation twice per day, and reliever as needed); (5) budesonide 200 µg plus formoterol 6 µg per inhalation as needed, and reliever as needed; and (6) salbutamol 100 µg per inhalation, and reliever as needed. We used Haillie sensors (Adherium, Auckland, New Zealand) to track inhaler use.

During screening and run-in, patients continued receiving benralizumab 30 mg every 8 weeks. At screening (visit 1), patients switched from their current ICS or long-acting β2-agonist maintenance treatment to high-dose budesonide 400 µg plus formoterol 12 µg, two inhalations twice per day, plus salbutamol 100 µg reliever treatment as needed. Patients continued this regimen for the 4–8-week screening and run-in period; the end of this period coincided with the next injection of benralizumab.

Maintenance of asthma control was defined as zero asthma exacerbations since the previous visit, no increase in ACQ-5 score[14] of 0·5 units or more compared with baseline (visit 1), and no significant increase in ICS–formoterol reliever use in the past 4 weeks (ie, a weekly average of >8 ICS–formoterol inhalations per day). Patients who maintained asthma control at the medium dose tapered their MART regimen either until they used ICS–formoterol as needed or until no further tapering was permitted owing to loss of asthma control (appendix p 12). Patients in the reference group continued high-dose

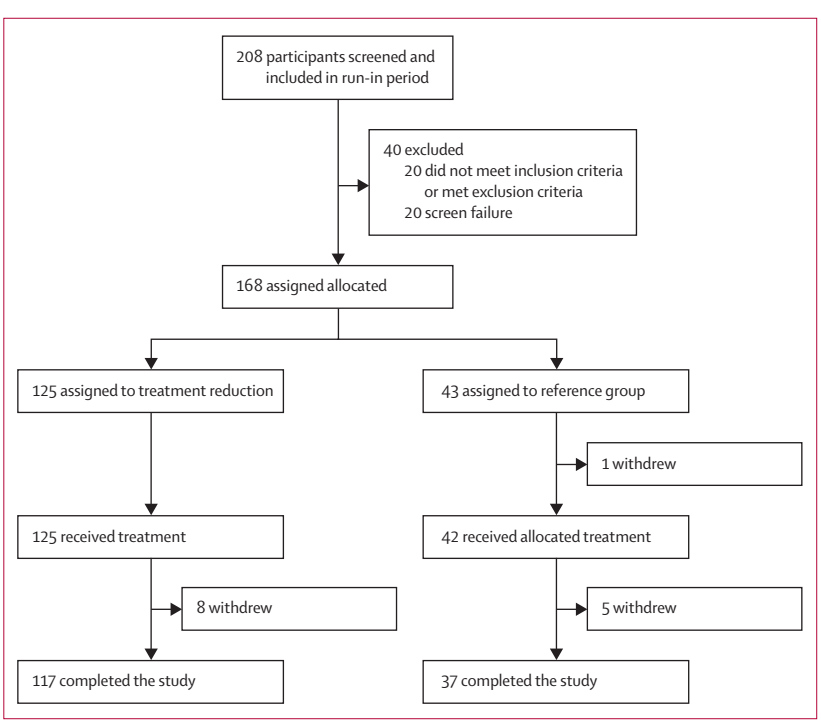

Figure 1: **Trial profile**

ICS–formoterol treatment and salbutamol reliever use as needed for the entire 32-week period. Following the reduction period, all patients entered the 16-week maintenance period, in which they continued their treatment regimen used at the end of the reduction period. No reductions in ICS–formoterol doses were permitted during the maintenance period, although increases could occur in the event of asthma worsening.

Electronic patient-reported outcomes included (1) ACQ-5 score, measured at screening and then weekly; (2) standardised asthma quality-of-life questionnaire for 12 years and older (AQLQ[S]+12) score, measured from visits 2b until 8b or the end of the study; and (3) patient perception of maintenance inhaler questionnaire score, measured at visits 2b, 6, and 8b or the end of the study. Physiological asthma assessments included pulmonary function tests (pre-bronchodilator forced expiratory volume in 1 s [FEV_1] and forced vital capacity) measured at visits 2b until 8b, excluding visit 8a, and FeNO measured at visits 2b until 8b, excluding visit 8a. Assessment of asthma exacerbations occurred throughout the study except for during visit 8a. We assessed safety and adverse events throughout the study period.

	Treatment reduction group (n=125)	Reference group (n=43)	Total (n=168)
Age, years	58·1 (12·44)	56·5 (11·70)	57·7 (12·24)
Age at asthma diagnosis, years	36·28 (18·81)	34·48 (22·11)	35·82 (19·65)
Sex			
Female	69 (55%)	20 (47%)	89 (53%)
Male	56 (45%)	23 (53%)	79 (47%)
Race			
White	95 (76%)	31 (72%)	126 (75%)
Black	1 (<1%)	1 (2%)	2 (1%)
Asian	0	2 (5%)	2 (1%)
Other	1 (<1%)	0	1 (<1%)
Not reported	5 (4%)	0	5 (3%)
Missing	23 (18%)	9 (21%)	32 (19%)
Non-Hispanic or non-Latino	91 (73%)	28 (65%)	119 (71%)
Country			
France	25 (20%)	9 (21%)	34 (20%)
Germany	56 (45%)	16 (37%)	72 (43%)
Italy	18 (14%)	6 (14%)	24 (14%)
UK	26 (21%)	12 (28%)	38 (23%)
Smoking status			
Former	45 (36%)	18 (42%)	63 (38%)
Never	80 (64%)	25 (58%)	105 (63%)
Blood eosinophil count (cells/μL)	0 (0–860)	0 (0–390)	0 (0–860)
Pre-bronchodilator FEV_1, L	2·26 (0·83)	2·32 (0·82)	2·27 (0·82)
Pre-bronchodilator FEV_1 (% predicted normal), L	75·92% (22·00)	75·67% (22·31)	75·85% (22·00)
FeNO, ppb	27·7 (18·82)	24·9 (19·46)	27·0 (18·94)
Exacerbations in 12 months before first commercial use of benralizumab	2·9 (3·29)	3·1 (2·68)	2·9 (3·13)
ACQ-5 score	0·54 (0·44)	0·50 (0·52)	0·53 (0·46)

Data are n (%), mean (SD), or median (range). Baseline measures in this study, except for exacerbation history, were taken following at least 8 weeks of benralizumab treatment and therefore represent a baseline response to benralizumab. ACQ-5=five-item Asthma Control Questionnaire. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 s. ICS=inhaled corticosteroids. Ppb=parts per billion.

Table 1: **Patient demographics and clinical characteristics**

Outcomes

The primary study endpoint was the proportion of patients who reduced their ICS–formoterol maintenance dose at the end of the reduction period (week 32) to either a medium-dose MART, a low-dose MART, or ICS–formoterol as needed. Secondary endpoints comparing the treatment reduction and reference groups included (1) change in ACQ-5 score from baseline to the end of the reduction period; (2) change in AQLQ(S)+12 score from baseline to the end of the reduction period; (3) the proportion of patients with no deterioration in AQLQ(S)+12 score (deterioration defined as a decrease of ≥0·5 units compared with baseline) at the end of the reduction period; (4) the proportion of patients with no deterioration in ACQ-5 score (deterioration defined as an increase of at least 0·5 unit compared with baseline) at the end of the reduction period; (5) change from baseline in pre-bronchodilator FEV_1 during the study period; (6) the annualised asthma exacerbation rate during the study period; (7) the cumulative total daily ICS dose (maintenance plus reliever) for the reduction period, maintenance period, and study period; (8) the total daily ICS dose (maintenance plus reliever) at the end of the reduction period; (9) the proportion of patients using the same ICS–formoterol daily dose at the end of the maintenance period (week 48) as that used at the end of the reduction period (week 32); (10) supportive outcomes, including the number of exacerbations occurring from the end of the reduction period to the end of the maintenance period, the total daily ICS dose from the end of the reduction period to the end of the maintenance period, and the change in ACQ-5 score, AQLQ(S)+12 score, and FEV_1 from the end of the reduction period to the end of the maintenance period; (11) the number and proportion of patients who met each composite criterion of clinical remission (no exacerbations, <10% deterioration in FEV_1, and ACQ-5 score <1·5 or ≤0·75) at visit 6 (week 32) and visit 8b (week 48); and (12) the number and proportion of patients who met zero, one, two, and all three remission components. Safety, adverse events, and serious adverse events were reported by the patient, caregiver, or patient's legally authorised representative and measured throughout the study period.

Statistical analysis

The target sample size was 240 patients screened to achieve 200 patients randomly assigned, assuming a screening failure of 15%. This sample size provided a nominal 95% CI around the observed proportions with a

half-width of less than 10 percentage points in the treatment reduction group.

This study included three patient populations: (1) an all-patients set, including all patients screened, to report disposition and screening factors; (2) a full analysis set, including all randomly assigned patients (including early study withdrawals) for efficacy analyses, demographics, and baseline characteristics; and (3) a safety analysis set, including all randomly assigned patients who received at least one dose of the study treatment, for all safety analyses.

We assessed the primary outcome of the ICS–formoterol maintenance dose prescribed at visit 6 (week 32) by calculating the proportion of patients at each step down together with exact two-sided 95% CIs (Clopper–Pearson method). We calculated ACQ-5 score, AQLQ(S)+12 score, and FEV_1 as post-baseline scores. We estimated the asthma exacerbation rate for each treatment group and presented with two-sided 95% CIs (Poisson model). The mean total daily ICS dose is presented by treatment group for each visit during the reduction and maintenance periods, together with two-sided 95% CIs calculated for the mean difference between groups. We assessed change from baseline in the mean total daily ICS dose (maintenance plus reliever; each visit and during the previous 8 weeks), change from baseline in ACQ-5 scores (each visit and during the previous 8 weeks), and FEV_1 scores (each visit) using a model for repeated measures, including baseline value, visit, treatment, and visit×treatment as fixed effects. We summarised safety data with descriptive statistics.

Additionally, we did sensitivity analyses excluding patients with important protocol deviations that could potentially affect the primary endpoint or lung function assessments. For the primary endpoint, these important protocol deviations mainly included the use of disallowed medication (such as strong CYP3A4 inhibitors), patients not meeting inclusion criteria (ie, no documented maintenance treatment along with high-dose

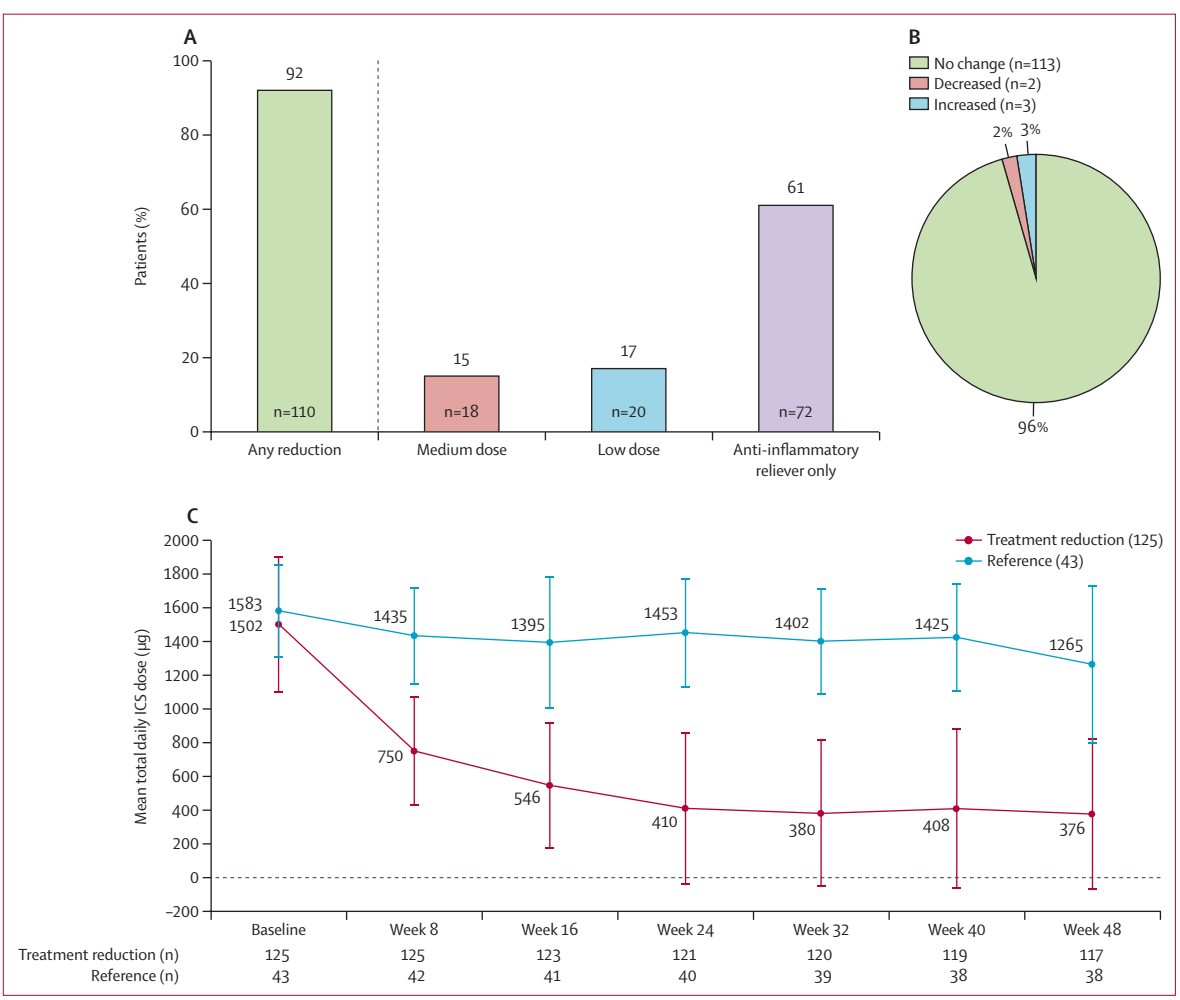

Figure 2: **Reductions in ICS–formoterol maintenance dose throughout the study**

(A) Patients reducing their ICS–formoterol maintenance dose at the end of the reduction period (week 32). (B) Patients maintaining their reduced dose throughout the maintenance period (week 48; n=118). (C) Changes in mean total daily ICS dose throughout the study. Proportions were calculated using the number of patients with a non-missing dose at week 32 and week 48 as the denominator. ICS=inhaled corticosteroids.

	Treatment reduction group	Reference group
ACQ-5 score change from baseline*	n=112	n=38
LS mean (SE)	0·16 (0·04)	0·06 (0·07)
LS mean difference (95% CI) *vs* reference	0·106 (–0·049 to 0·261)	..
AQLQ(S)+12 change from baseline*	n=99	n=35
LS mean (SE)	–0·03 (0·06)	0·01 (0·10)
LS mean difference (95% CI) *vs* reference	–0·034 (–0·253 to 0·184)	..
Patients with no deterioration in ACQ-5*†‡	93/108 (74%)	30/35 (70%)
Patients with no deterioration in AQLQ(S) + 12*†§	85/99 (68%)	31/35 (72%)
Pre-bronchodilator FEV_1 change from baseline, mL¶	n=92	n=29
LS mean (SE)	–88·9 (27·2)	5·9 (47·5)
LS mean difference (95% CI) *vs* reference	–94·7 (–202·9 to 13·4)	..
Cumulative total daily ICS dose, µg		
Reduction period	98 400 (400 to 397 000)	340 800 (24 800 to 416 800)
Maintenance period	33 000 (200 to 221 400)	164 000 (42 800 to 206 800)
Study period	113 800 (400 to 578 200)	501 800 (24 800 to 555 600)
Total daily ICS dose¶	n=117	n=38
Mean (SD)	376·36 (449·66)	1265·36 (472·52)
LS mean difference (95% CI) *vs* reference	–819·82 (–992·89 to –646·74)	..
Patients with no change in ICS–formoterol dose‖	113/118 (96%)	..
Total daily ICS dose‖	n=117	n=38
Mean (SD) change from maintenance period baseline	–3·69 (318·03)	–173·33 (459·79)
Change in ACQ-5‖	n=110	n=34
Mean (SD) change from maintenance period baseline	–0·07 (0·575)	–0·20 (0·814)
Change in AQLQ(S) + 12‖	n=97	n=31
Mean (SD) change from maintenance period baseline	–0·008 (0·47)	0·060 (0·57)
Change in FEV_1, mL‖	n=100	n=30
Mean (SD)	8·9 (232)	4·0 (226)

Data are n/N (%) or median (range), unless otherwise indicated. ACQ-5=five-item Asthma Control Questionnaire. AQLQ(S) + 12=standardised asthma quality of life questionnaire for 12 years and older. FEV_1=forced expiratory volume in 1 s. ICS=inhaled corticosteroid. LS=least squares. *Measurement taken at the end of the reduction period. †"No deterioration" includes patients with no change in score, as well as patients with an improvement in score. ‡25 (15%) of 168 patients had a missing value for this measure at week 32. §34 (20%) of 168 patients had a missing value for this measure at week 32. ¶Measurement taken at the end of the study period. ‖Measurement taken between the end of the reduction period and the end of the maintenance period.

Table 2: **Secondary endpoints**

ICS–formoterol), and dose reductions occurring at visit 6 (week 32) when reductions were no longer permitted after visit 5 (week 24). For the lung function endpoints, these important protocol deviations consisted of patients who did not withhold reliever therapy for at least 12 h before lung function assessments.

This trial is registered at ClinicalTrials.gov, NCT04159519.

Role of the funding source

All authors, including those employed by the funder, participated in the study design, data collection, data interpretation, and writing of the report. AstraZeneca reviewed the manuscript, without influencing the opinions of the authors, to ensure medical and scientific accuracy and the protection of intellectual property.

Results

Between Nov 12, 2019, and Feb 16, 2023, we screened and enrolled 208 patients with controlled severe eosinophilic asthma receiving high-dose ICS–formoterol and benralizumab in the run-in period; we randomly assigned 168 patients to the reduction phase (figure 1; appendix p 13). We randomly assigned 125 (74%) patients to treatment reduction and 43 (26%) to the reference group (figure 1). Of those 168, 154 (92%) patients completed the study and 14 (8%) discontinued; the most common reasons for study discontinuation were withdrawal (eight [5%]), adverse events (two [1%]), protocol deviation (two [1%]), lack of efficacy (one [<1%]), and other (one [<1%]).

The mean patient age was 57·7 years (SD 12·2), 89 (53%) were female, 79 (47%) were male, and 126 (75%) were White. The baseline mean FeNO concentration was 27·0 parts per billion (ppb; 18·94) and the mean pre-bronchodilator FEV_1 was 2·27 L (0·82; table 1). 110 (92%) of 119 patients reduced their ICS–formoterol maintenance dose at the end of the reduction period (week 32; figure 2A): 18 (15%) to medium-dose ICS–formoterol, 20 (17%) to low-dose ICS–formoterol, and 72 (61%) to ICS–formoterol reliever

only. In the reduction group, 113 (96%) of 118 patients with a non-missing dose maintained the same ICS–formoterol daily dose from the end of the reduction period (week 32) until the maintenance period conclusion (week 48; figure 2B). The mean change from baseline in total daily ICS dose (maintenance plus reliever) from randomisation to the end of the study was –1171 µg (SE 43·33) in the reduction group and –351 µg (76·06) in the reference group; the least-squares (LS) mean difference in change from baseline at week 48 between the two arms was –819·82 (95% CI –992·89 to –646·75; figure 2C). When patients with important protocol deviations affecting the primary endpoint were excluded (sensitivity analysis; n=23 [18%] in the treatment-reduction group), 13 (14%) reduced to a medium dose, 17 (18%) reduced to a low dose, and 57 (59%) reduced to ICS–formoterol reliever only. Overall, the mean changes in total daily ICS doses between reduction and maintenance periods (week 32–48) were –3·69 (318·03) for the reduction group and –173·33 (459·79) for the reference group (table 2).

The LS mean change from baseline to week 32 in ACQ-5 scores was 0·16 (SE 0·04) in the reduction group and 0·06 (0·07) in the reference group (appendix p 14). The LS mean change from baseline to week 32 in AQLQ(S)+12 score was –0·03 (0·06) in the reduction group and 0·01 (0·10) in the reference group (table 2). By week 32, in the reduction group, 93 (74%) patients had no deterioration in ACQ-5 score and 85 (68%) had no deterioration in AQLQ(S)+12 score and, in the reference group, 30 (70%) had no deterioration in ACQ-5 score and 31 (72%) had no deterioration in AQLQ(S)+12 score. Changes between weeks 32 and 48 were minimal (table 2).

Annualised asthma exacerbation rates (AERs) were similar between groups (table 3). At the end of the entire study period, the AER was 0·14 (95% CI 0·09–0·23) in the reduction group and 0·14 (0·06–0·31) in the reference group (rate ratio 1·05 [0·41–2·68]). During the reduction period, AERs were 0·15 (0·08–0·26) in the reduction group and 0·04 (0·01–0·28) in the reference group; during the maintenance period, AERs were 0·14 (0·06–0·33) in the reduction group and 0·35 (0·14–0·90) in the reference group (table 3). Most patients were exacerbation-free throughout the study period (109 [87%] in the reduction group and 38 [88%] in the reference group).

The LS mean change from baseline in pre-bronchodilator FEV_1 at the end of the study was –88·9 mL (SE 27·2) in the reduction group and 5·9 mL (47·5) in the reference group (figure 3A). The mean change in FEV_1 between week 32 and week 48 was 9 mL (SD 232) in the reduction group and 4 mL (226) in the reference group. Mean FeNO concentrations at the end of the study were 48·8 ppb (41·10) in the reduction group and 27·8 ppb (18·71) in the reference group. The LS mean changes in FeNO concentrations by the end of the study were 22·92 ppb (3·33) in the reduction group and 3·41 ppb (5·72) in the reference group (figure 3B). In a post-hoc analysis of groups stratified by ICS–formoterol dose at week 32, patients who reduced to reliever only had the largest LS mean change from baseline in FEV_1 (–146·7 mL [34·6]; figure 3C) and FeNO concentrations (31·99 ppb [4·09]; figure 3D) by week 48, compared with all others; changes in other groups were modest (eg, low-dose ICS; figure 3C, D). The LS mean difference for the reliever-only group compared with the reference group was –153·5 mL (95% CI –269·6 to –37·5) in FEV_1 and 28·97 ppb (15·23 to 42·70) ppb in FeNO (figure 3).

We did a sensitivity analysis following the identification of important protocol deviations among patients. This analysis excluded patients who did not withhold reliever therapy for at least 12 h before lung function assessments. Minor differences were observed in FEV_1 and FeNO analyses compared with the primary analysis (appendix p 23). The LS mean change from baseline in pre-bronchodilator FEV_1 at the end of the study was –101·9 mL (SE 29·1) in the reduction group and –8·7 mL (51·9) in the reference group (appendix p 15). LS mean changes in FeNO concentrations at the end of the study were 24 ppb (3·62) in the reduction group and 3·92 ppb (6·34) in the reference group (appendix p 15). In a post-hoc analysis of patients stratified by their ICS–formoterol dose at week 32, LS mean changes from baseline in pre-bronchodilator FEV_1 and FeNO concentration were similar among patients in the sensitivity analysis (appendix p 16).

An additional post-hoc analysis revealed that the mean number of reliever inhalations per week among patients reducing to reliever only by week 32 was 6·3 (SD 7·87). Patients using fewer than five inhalations per week had the largest LS mean change from baseline at week 48 in both FEV_1 (–223·5 [SE 49·1] mL) and FeNO concentration (35·57 ppb [5·82]); patients using five or more inhalations per week had changes of (–70·5 [51·8] mL) in FEV_1 and (27·64 ppb [6·17]) in FeNO concentration (appendix p 17). Compared with the reference group, the LS mean difference was –230·1 mL

	Exacerbations, n	Total follow-up, years	Annual exacerbation rate (95% CI)	Rate ratio (95% CI)
Reduction period				
Treatment reduction (n=125)	11	75·54	0·15 (0·08–0·26)	3·67 (0·49–27·55)
Reference (n=43)	1	25·19	0·04 (0·01–0·28)	..
Maintenance period				
Treatment reduction (n=125)	5	35·96	0·14 (0·06–0·33)	0·39 (0·11–1·39)
Reference (n=43)	4	11·32	0·35 (0·14–0·90)	..
Entire study period				
Treatment reduction (n=125)	16	111·83	0·14 (0·09–0·23)	1·05 (0·41–2·68)
Reference (n=43)	5	36·61	0·14 (0·06–0·31)	..

Table 3: **Annualised exacerbation rates throughout the study period**

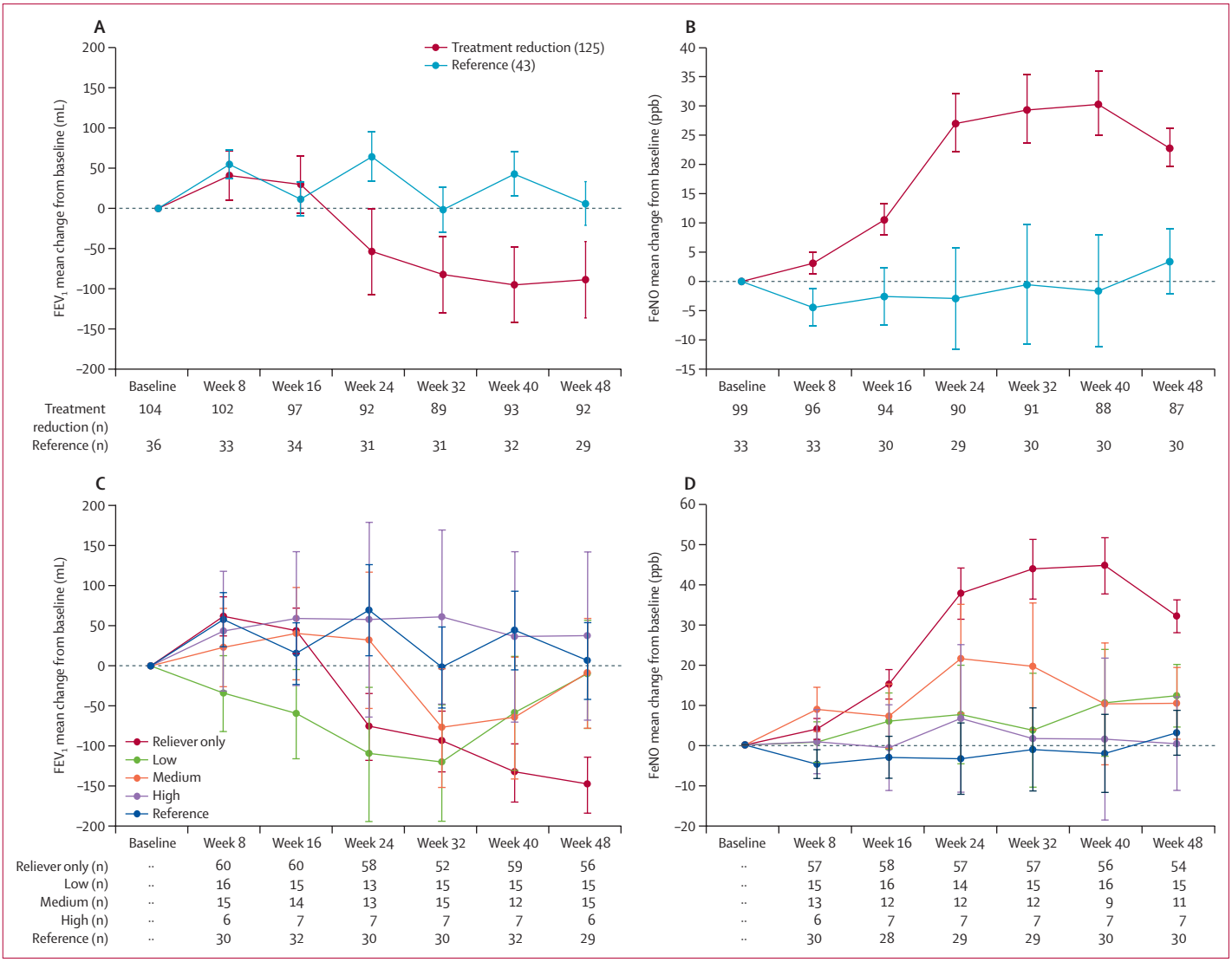

***Figure 3*: Change from baseline in pre-bronchodilator FEV_1 and FeNO**

Figure shows changes throughout the study period (A, B) and when stratified by week 32 ICS–formoterol dose (C, D). Error bars denote SEs. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 s. ppb=parts per billion.

(95% CI −366·5 to −93·7) in FEV_1 and 32·69 ppb (16·46 to 48·91) ppb in FeNO concentration in those using fewer than five inhalations per week, and −77·1 mL (−217·4 to 63·1) in FEV_1 and 24·75 ppb (8·03 to 41·48) in FeNO concentration in those using five or more inhalations per week. Assessments of relationships between change from baseline in FEV_1 and change in FeNO concentration in the reduction group revealed weak but statistically significant correlations at weeks 32 (−0·39; p=0·0003) and 48 (−0·24; p=0·024); a similar statistically significant correlation was observed between change from baseline in FEV_1 and absolute FeNO concentration at week 32 (−0·24; p=0·027) but not at week 48 (−0·16; p=0·12; appendix p 18). Analyses of correlations between change from baseline in FEV_1 and absolute FeNO concentration in patients using anti-inflammatory reliever only by week 32 were not significant (appendix p 19).

Clinical remission occurred in the reduction group in 48 (56%) patients at week 32 and 48 (54%) patients at week 48 (ACQ-5 score <1·5). Differences were minimal when we excluded patients with important protocol deviations affecting lung function assessments from remission analyses (data not shown). Patients who met each remission component and the composite endpoint at weeks 32 and 48 are summarised in the appendix (p 20). The patient perception of maintenance inhaler questionnaire highlighted that at week 32 most patients in the reduction group strongly agreed that their current inhaler therapy was easy to use (n=61; 73%), that it worked to manage asthma (n=55; 66%), and that it relieved their asthma symptoms (n=43; 51%). These

positive responses were maintained by the end of the maintenance phase at week 48 (appendix pp 21–22). Blood eosinophil concentrations were generally similar between treatment groups and over time throughout the duration of the study (appendix p 24).

Rates of adverse events were similar between groups throughout the study. 91 (73%) patients had adverse events in the reduction group and 35 (83%) in the reference group. 17 patients had serious adverse events in the study: 12 (10%) in the reduction group and five (12%) in the reference group (appendix p 25). None of the serious adverse events in the reduction group occurred in 1% or more of patients. There were no deaths during the study (appendix p 25).

Discussion

In the SHAMAL study, we investigated whether continued high doses of ICS are necessary for patients with severe asthma following reaching symptom control with benralizumab. Our key finding is that 92% of patients were able to successfully reduce their high-dose ICS, with more than 60% reducing to anti-inflammatory reliever only without a change in asthma control. Additionally, despite substantial ICS reductions, more than 87% of patients remained exacerbation-free by week 48 in the treatment-reduction group. In this first clinical study prospectively assessing clinical remission among patients with severe eosinophilic asthma, more than half of patients reducing background medications met the definition for clinical remission at week 48. We found a decline in FEV_1 in some patients reducing their ICS to as-needed only. Finally, we found a small but significant correlation between the change in lung function and change in FeNO concentration among all patients in the treatment-reduction group.

National and international treatment guidelines recommend escalation to high-dose ICS for patients with severe asthma failing to respond to lower ICS doses. Ongoing poor disease control and the need for frequent bursts or daily use of OCS despite this step are most frequently seen in patients with a severe ICS-resistant eosinophilic phenotype. For these individuals, initiation of biologic therapies that target eosinophilic inflammation, such as benralizumab, has led to substantially improved clinical outcomes, allowing most to become OCS-free.[9,15] However, there has also been concern regarding prolonged use of high-dose ICS, with some evidence showing dose-related increased risks of adverse events, including adrenal suppression, cataracts, osteoporosis-related fractures, and diabetes.[8] In light of this concern, GINA[3] recommends that clinicians reduce ICS doses in patients with severe asthma who respond positively to biologics, despite the lack of evidence to support the safety and clinical efficacy of this recommendation. SHAMAL, therefore, represents the most comprehensive study to date in support of this recommendation and builds on the results of the preliminary, single-arm, open-label ANDHI–In Practice sub-study, in which more than half of patients with severe eosinophilic asthma controlled on benralizumab were able to reduce their high-dose ICS while maintaining asthma control.[16]

The therapeutic value of high-dose ICS in asthma is a subject of ongoing debate because the evidence base for the step-wise intensification of ICS dose in patients with asthma is mixed, with maximum clinical benefits of ICS appearing at a low dose.[8,17] However, a biologic-eligible population with more severe asthma was not the primary population of these studies, and data from phase 3 trials and other studies clearly show lower exacerbation rates and improved lung function at high-dose versus medium-dose ICS,[18,19] as well as a substantial reduction in blood eosinophil count following an increase from medium-dose to high-dose ICS in patients with severe asthma.[20] As such, one cannot assume that an increase to high-dose ICS is either without value in some patients, or that the results of this study will be equally applicable to all asthma biologic therapies. Notably, real-world analyses of the clinical implications of poor adherence to daily ICS therapy following initiation of benralizumab[21] and mepolizumab[22] highlighted a differential response with an increase in exacerbations in the mepolizumab cohort, but not in the benralizumab cohort, following an unscheduled decrease in ICS use. Conceivably, this finding might reflect the differential degree of tissue eosinophil depletion with these two therapies,[23,24] a hypothesis supported by the finding that 50% of exacerbations occurring in patients on mepolizumab still have eosinophilic inflammation.[25] Consequently, similar studies to SHAMAL will be necessary with other asthma biologic therapies before firm recommendations can be made regarding the safety and efficacy of ICS withdrawal for therapies with a different mechanism of action than that of benralizumab.

From a mechanistic perspective, the eosinophil-depleting effect of benralizumab has provided SHAMAL with a unique opportunity to expand our understanding of type 2 biology in severe asthma, allowing insights into the clinical relevance of eosinophil-independent, ICS-responsive, inflammatory mediators that are not suppressed by targeting the IL-5 receptor. The finding that most patients remained exacerbation-free and had good symptom control on anti-inflammatory reliever therapy only, despite variable degrees of lung function decline over the course of the study, is interesting from a mechanistic perspective and is also clinically important. The implications of this airway inflammation in asymptomatic patients and the independent roles of eosinophilic versus non-eosinophilic type 2 inflammation are not well understood.[26,27] The results support a delineation between eosinophilic inflammation driving exacerbations and poor symptom control and non-eosinophilic—but ICS-responsive—inflammation leading to lung function decline.

This study has some limitations. First, the patients eligible for this study had already responded well to

benralizumab and, therefore, had a demonstrably eosinophil-driven phenotype. Some patients with severe eosinophilic asthma respond to a lesser extent to benralizumab, and a reduction to low-dose ICS in these patients might be less well tolerated owing to the activity of non-eosinophil-mediated type 2 signalling. Second, an important consideration relating to the observed lung function results is the possibility of a suboptimal formoterol washout (defined in the protocol as a minimum of 12 h before FEV_1 measurements at study visits). Although the maximal bronchodilator effect of formoterol is within the first 12 h, evidence suggests some residual effect beyond 12 h.[28] All patients other than those on an anti-inflammatory reliever would have had daily formoterol within 24 h of the FEV_1 measurement. Nevertheless, the statistically significant correlation between lung function decline and change in FeNO concentration suggests that this explanation is unlikely to be the major contributing factor. We also note that this study occurred during the COVID-19 pandemic, which might have contributed to the low rates of annualised exacerbations. Furthermore, the run-in and follow-up periods in this study were short and the controlled trial setting differs from routine clinical practice. Finally, although we showed the efficacy of this approach to reducing ICS dose in this population, effectiveness outcome measures were not part of the study design.

Targeting eosinophils with benralizumab has previously been shown to reduce systemic steroid exposure in severe asthma. SHAMAL now provides evidence that exposure to high-dose ICS can also be minimised by this therapeutic approach. The data further cement the central role of eosinophils in exacerbation pathogenesis and symptom control; however, the relationship between the decline in lung function and increase in FeNO concentration in those reducing regular ICS suggests this might be an eosinophil-independent, IL-13-driven process. Although we were unable to further delineate sub-phenotypes of severe eosinophilic asthma, these results favour the continuation of low-dose ICS in patients for whom combined assessments of changes in FEV_1 and FeNO concentration suggest an increased risk of lung function decline.

Contributors

DJJ, LGH, MH, BDK, AS, AM-G, and SK contributed to the study conception and design. LH, LO, and DC contributed to the statistical analyses, data entry, and verification. All authors were involved in the study implementation, data acquisition, and interpretation of the results. All authors critically reviewed the manuscript, approved the final version for submission, and agree to be accountable for all aspects of this work.

Declaration of interests

DJJ has received advisory board and speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Sanofi. LGH has received grant funding, participated in advisory boards, and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Evelo Biosciences, GSK, Hoffmann-La Roche, Novartis, Sanofi, Teva, and Theravance; he has received grants from Aerocrine, Amgen, AstraZeneca, Genentech/Hoffman-La Roche, GSK, MedImmune, Novartis UK, Roche/Genentech, and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, GSK, and Hoffmann-La Roche, for which his institution received remuneration; he is the academic lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies, including Amgen, AstraZeneca, Boehringer Ingelheim, GSK, Hoffmann-La Roche, and Janssen. MH has received consulting fees from AstraZeneca, Chiesi, GSK, Novartis, and Sanofi. BDK has participated in advisory boards or received speaker fees from AstraZeneca, Chiesi, GSK, Novartis, and Teva; has received educational travel bursaries from Boehringer Ingelheim, Chiesi, and Napp Pharmaceuticals; and has received research funding from Itamar Medical. AS was an employee of AstraZeneca at the time of this study and may own stock. LH was an employee of AstraZeneca at the time of this study and may own stock. LO is an employee of Cytel and was on contract to AstraZeneca at the time of this study. DC was an employee of AstraZeneca at the time of this study and may own stock. AM-G was an employee of AstraZeneca at the time of this study and may own stock; has attended advisory boards for AstraZeneca, GSK, Novartis, Regeneron, Sanofi, and Teva; has received speaker fees from AstraZeneca, Novartis, Sanofi, and Teva; has participated in research with AstraZeneca, for which his institution was remunerated; and has had consultancy agreements with AstraZeneca and Sanofi. SK has received grants and personal fees for lectures and advisory boards from AstraZeneca, GSK, Novartis, Sanofi-Genzyme, and Teva.

Data sharing

Data underlying the findings described in this manuscript can be requested in accordance with AstraZeneca's data sharing policy described online at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at https://www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. Further details are available online at https://vivli.org/ourmember/astrazeneca/.

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