EFFECT OF DIFFERENT ASTHMA TREATMENTS ON RISK OF COLD-RELATED EXACERBATIONS

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ABSTRACT

Common colds often trigger asthma exacerbations. This analysis compared cold-related severe exacerbations during budesonide/formoterol maintenance and reliever therapy and different regimens of maintenance inhaled corticosteroid (ICS) ± long-acting β₂-agonist (LABA) with as-needed short-acting β₂-agonist (SABA) or LABA.

Reported colds, and severe exacerbations (defined by oral corticosteroid use and/or hospitalisation/emergency room visit) were assessed for 12507 patients during 6–12 months’ double-blind treatment. Exacerbations occurring ≤14 days after onset of reported colds were analysed by a Poisson model.

Incidence of colds was similar across treatments. Asthma symptoms and reliever use increased during colds. Budesonide/formoterol maintenance and reliever therapy reduced severe cold-related exacerbations by 36% versus pooled comparators plus SABA (rate ratio [RR] 0.64; \( P=0.002 \)), and, for individual treatment comparisons, by 52% versus same maintenance dose ICS/LABA (RR 0.48; \( P<0.001 \)); there were non-significant reductions versus higher maintenance doses of ICS or ICS/LABA (RR 0.83 and 0.72). As-needed LABA did not reduce cold-related exacerbations versus as-needed SABA (RR 0.96).

Severe cold-related exacerbations were reduced by budesonide/formoterol maintenance and reliever therapy compared with ICS±LABA with as-needed SABA. Subanalyses suggest the importance of the ICS component in reducing cold-related exacerbations. Future studies should document the cause of exacerbations, to allow identification of different treatment effects.
INTRODUCTION

Asthma is unusual amongst chronic diseases, in that severe exacerbations occur even in mild or well-controlled disease. This paradox is largely attributable to viral respiratory infections causing clinical colds, which, although no more common in asthma [1], cause more prolonged and severe lower respiratory symptoms [1, 2] and are responsible for 50–75% of asthma exacerbations in adults [3]. During confirmed viral infections, there is an influx of inflammatory cytokines and chemokines and inflammatory cells, particularly neutrophils [2, 4]. As asthma is common and viral respiratory infections are ubiquitous, even a low rate of exacerbations in individual patients contributes substantially to the economic burden of asthma. This is reflected in recent guidelines, with increasing focus on exacerbations and costs/risks of treatment as well as on patient-centred outcomes such as symptoms and quality of life.

While the reduction in all-cause exacerbations with inhaled corticosteroids (ICS) alone or with long-acting \( \beta_2 \)-agonists (LABA) is well established [5], little is known about effects on cold-related exacerbations. In the past, exacerbations have been studied with ICS-reduction [6] or allergen challenge models [7], but there is increasing recognition that viral exacerbations have different clinical and inflammatory features [4, 8, 9]. The effect of pharmacological agents, including ICS, therefore cannot be assumed to be the same for cold-related and non-cold-related exacerbations.

Asthma clinical trials only rarely document causes of exacerbations, and few include viral sampling, so information about therapeutic effects during clinical colds is largely limited to \textit{in vitro} rhinovirus studies [10-12]. However, adverse events (AEs), including clinical colds, are prospectively recorded at study visits with a standardised question such as “Have you had any health problems since your last visit?”. Pooled AE records were recently used to demonstrate a reduced risk of cold-related exacerbations with ICS/LABA compared to ICS alone [13].
Clinical practice guidelines focus on reducing exacerbations, not only with maintenance therapy, but also by providing patients with written action plans [14]. Key components of effective action plans include increasing ICS after asthma worsens [15]. However, since the emergence of placebo-controlled evidence that doubling ICS does not reduce progression to exacerbation [16], guidelines currently recommend increasing short-acting $\beta_2$-agonist (SABA) for symptom relief, with no additional anti-inflammatory treatment unless the episode progresses to a severe exacerbation and oral corticosteroids (OCS) are required [17, 18]; on average this is 5–10 days after asthma symptoms first start to increase [19, 20]. An alternative regimen, examined in recent large randomised controlled trials [21-25], uses budesonide/formoterol as maintenance therapy, with extra inhalations of budesonide/formoterol (80/4.5 or 160/4.5μg) as-needed for relief of asthma symptoms, regardless of their cause. The “action plan” for this treatment regimen thus includes an increase in both ICS and rapid-onset LABA, rather than SABA, as soon as symptoms and bronchoconstriction worsen. This regimen has been shown to reduce all-cause exacerbations with similar or better levels of asthma control than double-blind comparators [26], but its effect during colds has not been studied.

The present retrospective analysis therefore investigated the association between reported colds and severe asthma exacerbations amongst 12507 patients who participated in five large clinical trials, and the extent to which different treatments prevented cold-related exacerbations.

METHODS

Studies and population

This retrospective analysis included five double-blind, randomised, parallel-group clinical studies of 6–12 months’ duration, running across summer and winter periods in northern and southern hemispheres, investigating the efficacy of budesonide/formoterol maintenance and reliever therapy (Symbicort SMART® Turbuhaler® AstraZeneca AB, Lund, Sweden). Eligible
patients were prescribed GINA Step 2–4 treatment pre-entry, with ≥1 asthma exacerbation in the previous year, bronchodilator reversibility, and suboptimally controlled asthma during run-in. Time to first severe exacerbation was the primary end point for all studies. All studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by independent ethics committees. See online supplement for further details (Table E1).

For the primary analyses, pooled data from budesonide/formoterol maintenance and reliever therapy, with reliever doses of 80/4.5 or 160/4.5μg, were compared with pooled data from three comparator regimens of fixed-dose maintenance treatment, namely higher maintenance dose ICS [21, 22], same-dose maintenance ICS/LABA [22, 23] and higher-dose maintenance ICS/LABA [24, 25], each with as-needed SABA (details and doses in Table E1). Similar analyses were also performed with each of the individual maintenance regimens.

For one study [23], data from a third treatment arm with same-dose ICS/LABA plus as-needed formoterol (4.5μg Oxis® Turbuhaler, AstraZeneca, Sweden) were excluded from the main analyses, but a subanalysis comparing budesonide/formoterol maintenance and reliever therapy with same-dose ICS/LABA plus as-needed SABA or LABA was performed.

For seasonal analysis, each country was classified as northern or southern hemisphere, excluding Brazil, India, Indonesia, Malaysia, Philippines, Singapore, Thailand and Vietnam, which were defined as tropical countries; northern hemisphere ‘summer’ was defined as March–August and ‘winter’ as September–February, with the reverse for the southern hemisphere.

**Assessments**

*Reported common colds*

Reported common colds with onset after randomisation were captured by searching AEs,
recorded at 3-monthly study visits, for the following Preferred Terms in MedDRA version 10: *upper respiratory tract infection (URTI)*; *viral URTI*; *pharyngitis*; *viral pharyngitis*; *nasopharyngitis*; *laryngopharyngitis*. For each reported cold, the date of onset was defined as the ‘cold index day’, and the following 14 days as the ‘cold period’.

**Exacerbations**

A severe exacerbation was defined as deterioration in asthma resulting in OCS use for $\geq 3$ days and/or hospitalisation/emergency room treatment. The prescription of OCS was according to the clinical judgement of the physician, who was unaware of the patient’s [double-blind] treatment allocation. Milder exacerbations, and those identified in two studies [21, 22] only by a fall in morning peak flow were excluded.

**Reliever use and asthma symptoms**

As-needed reliever use and asthma symptom score were recorded in patient diaries. Daily asthma symptom score (0–6) was the sum of night- and daytime scores (0=no symptoms, 3=unable to do normal activities or to sleep).

**Statistical methods**

All patients with recorded post-randomisation data were included in the analysis. Monthly rates of all reported colds and exacerbations were described by plots. As a stability check, similar plots were produced for MedDRA diagnostic codes of *conjunctivitis allergic*, *rhinitis allergic* or *rhinitis seasonal*, and for all non-infectious AEs excluding allergy and asthma-related AEs.

The number of exacerbations in each season was analysed in a Poisson model for correlated within-patient observations, with factors treatment, season, treatment–season interaction, hemisphere, hemisphere–season interaction and study, with (log-transformed) observation time as an offset.
The number of exacerbations for cold periods and non-cold periods was analysed using a Poisson model with factors treatment, cold status (cold period/non-cold period), treatment–cold status interaction, geographic area and study. Results were compared with a number of alternative models including Cox models for time to exacerbation with season or cold status as time-dependent factors (see online supplement).

For patients with a reported cold, exacerbation incidence in Days 0–14 after the patient’s first reported cold was described by Kaplan–Meier plots and analysed using a Cox proportional hazard model for time from onset of cold to first exacerbation, censored after 14 days. For patients with a reported cold, with or without an exacerbation in the cold period, mean asthma symptom score and reliever use were plotted for Days –7 to 21 relative to the first cold index day.
RESULTS

Patient characteristics

The analysis set comprised 12507 patients (86% adults) with 66% from the northern hemisphere (Table 1, online Table E2). Patients had characteristics of poorly-controlled asthma at randomisation. Patients from different geographic areas showed some differences in baseline characteristics, including time from diagnosis, pre-entry LABA use, and reliever use during run-in (Table 1). However, baseline data were comparable between treatment groups (online Table E2). Allergic conditions (rhinitis and/or conjunctivitis) were recorded as concomitant conditions at baseline for 22-34% patients (average 28% across studies), well-matched between treatment groups.

Incidence of reported colds

The incidence of reported colds was driven almost exclusively by reports of URTI, pharyngitis, and nasopharyngitis. Fewer colds were reported from northern hemisphere sites than southern and tropical sites (0.29, 0.39 and 0.49/patient/year, respectively). In the main analyses, rates and numbers of colds were similar across treatments, reported by 20–22% patients in 1-year studies (Table 2). Median duration of reported colds was 7 days (interquartile range 5–11).

Reported colds, allergic episodes and all-cause exacerbations by season

Reported colds and all-cause exacerbations displayed a similar seasonal pattern, with winter peaks in both hemispheres, lower in northern- than southern-hemisphere countries (Figures 1A, B). Non-infectious AEs were stable throughout the year in both hemispheres (Figure 1C), with lower reporting rates from northern- compared with southern-hemisphere countries [27]. The incidence of allergic rhinitis and allergic conjunctivitis AEs was low compared with colds, with a different peak (northern: April/May; southern: October, Figure 1D). There were
too few children/adolescents to examine seasonal patterns separately.

The rate of severe exacerbations was significantly lower with budesonide/formoterol maintenance and reliever therapy (9–13%) compared with pooled and individual fixed dose maintenance treatments plus as-needed SABA (12–22%) (Table 2). During both summer and winter periods, significantly fewer exacerbations occurred with budesonide/formoterol maintenance and reliever therapy compared with pooled treatment comparators plus SABA (Figure 1, Table E3, \( P<0.001 \)) and also compared with most individual treatment comparators (Figure E1, all \( P<0.001 \)). The exception was in the comparison with higher maintenance dose ICS/LABA plus SABA, where there was a significant reduction in all-cause exacerbations with budesonide/formoterol maintenance and reliever therapy during winter (41%, rate ratio [RR] 0.59 [95% CI: 0.46–0.76]; \( P<0.001 \)) but no significant reduction during summer (14%, RR 0.86 [95% CI: 0.63–1.18]; \( P = 0.35 \), online Figure E1).

**Severe exacerbations following onset of a reported cold**

The proportion of patients with an exacerbation within the week before a reported cold was low (<0.2% across all groups) but increased rapidly post-index day by approximately ninefold (Table 3), with 10% of severe exacerbations occurring during reported cold periods. During cold periods, budesonide/formoterol maintenance and reliever therapy significantly decreased the risk of severe exacerbations, with a 36% reduction compared with pooled fixed-dose maintenance treatments plus SABA (RR 0.64 [95% CI: 0.48–0.84]). For individual treatment comparisons (Table 3), the greatest reduction in cold-related exacerbations was with budesonide/formoterol maintenance and reliever therapy compared with same maintenance dose ICS/LABA plus SABA (52% reduction, RR 0.48 [95% CI: 0.31–0.72]), with non-significant reductions in cold-related exacerbations with budesonide/formoterol maintenance and reliever therapy compared with higher maintenance dose ICS plus SABA (17% reduction, RR 0.83 [95% CI: 0.49–1.40]) and higher maintenance dose ICS/LABA plus SABA (28% reduction, RR 0.72 [95% CI: 0.45–1.15]).
For time to first severe asthma exacerbation from the first cold index day, budesonide/formoterol maintenance and reliever therapy was also superior when compared with pooled fixed dose maintenance treatments plus SABA, and compared with same maintenance dose ICS/LABA plus SABA (Figures 2, 3).

In the comparison of cold versus non-cold periods, there was no significant difference in exacerbation rate reduction with budesonide/formoterol maintenance and reliever therapy relative to pooled comparators (36% relative reduction in cold periods vs. 43% in non-cold periods, RR 1.12 [95% CI 0.83–1.50]; \( P=0.47 \)). Cold periods comprised only 2.7 weeks/patient/year, so there was limited power for individual treatment comparisons, but compared with high-dose ICS, the magnitude of reduction in exacerbations with budesonide/formoterol maintenance and reliever therapy was smaller in cold periods than non-cold periods (17% vs. 47%, RR 1.56 [95% CI: 0.91–2.69], \( P=0.11 \)).

For patients taking the same maintenance dose of ICS/LABA but different reliever medications (Figure 3, Table E5), the comparison of exacerbation rate and time to first exacerbation showed that as-needed budesonide/formoterol was significantly better than either as-needed SABA or as-needed LABA during both cold and non-cold periods. For the comparison between as-needed SABA and as-needed LABA, there was no difference during cold periods in either exacerbation rate or time to first exacerbation (Figure 3, Table E5), whereas during non-cold periods, there were significant differences favouring as-needed LABA (Table E5).

**Reliever use and asthma symptoms in association with reported colds**

During reported colds, mean as-needed reliever use increased, particularly during severe exacerbations (Figure 4). For patients reporting a cold, those with a cold-related exacerbation had higher reliever use, averaged over the whole study, than those without a post-cold exacerbation. Asthma symptoms showed a similar pattern (data not shown). Reliever use for the individual comparators is shown in Figure E2.
DISCUSSION

This retrospective analysis of a large clinical trial dataset confirmed that, even with highly effective treatment regimens, clinical colds remain an important trigger for severe asthma exacerbations, particularly during winter. Colds occurred at a similar rate with different controller treatment regimens, but budesonide/formoterol maintenance and reliever therapy reduced the risk of severe cold-related exacerbations by 36% compared with pooled comparator regimens in which the reliever medication was SABA. The greatest difference in cold-related exacerbations (52%) was seen in the comparison with same-dose maintenance ICS/LABA, where the only treatment difference was that, as symptoms increased, patients received additional ICS/LABA rather than additional SABA. These findings, together with those of other subgroup analyses, are consistent with current knowledge about the inflammatory milieu of the airways during viral infections and with increasing evidence for the role of ICS dose in the management of worsening asthma.

Results from retrospective analyses should be interpreted with caution. In this study, viral causation of exacerbations was not proven, although strongly suggested by clinical diagnoses consistent with the common cold. No information was available about allergic sensitisation or allergen exposure, and even in prospective studies, as in clinical practice, it may be difficult to establish the relative contribution of viruses and allergen to individual exacerbations. AE data may be affected by patient recall or, as suggested by the geographic differences in the present study, by variation between clinical trial sites in the rigor with which they are recorded [27]. However, with AEs collected prospectively in randomised trials, bias, if any, is likely to be similar between groups. The rate of reported colds was lower than in prospective studies (0.33–0.34 vs. 1.2–6.7/patient/year [28]), and only 10% of severe exacerbations were during cold periods, suggesting that many associated colds were not reported, or that the selected diagnostic codes lacked sensitivity. However, their specificity is supported by the winter peak in both hemispheres which contrasted with the spring-time peak for allergic rhinitis/conjunctivitis, the contemporaneous increase in diary records for asthma symptoms and reliever use, and the marked increase in severe exacerbations after cold onset.

A strength of the present dataset was the opportunity to analyse cold-related exacerbations with four different treatment comparisons, and these analyses were instructive. While the halving of cold-related exacerbations with budesonide/formoterol maintenance and reliever therapy compared with same maintenance dose ICS/LABA plus as-needed SABA could potentially have been explained by the reliever’s LABA component, this was not supported by a similar difference (54%) between as-needed ICS/LABA and as-needed LABA, and the lack of evidence during colds for differences between as-needed LABA and SABA. However, a more consistent pattern was seen with ICS dose: the greatest difference in cold-related exacerbations with budesonide/formoterol maintenance and reliever therapy (52%) was seen versus same-dose maintenance ICS/LABA (mean total ICS dose 582 vs. 389µg BDP CFC-equivalent), with smaller non-significant differences as the relative ICS dose in the comparator arm increased (28% reduction vs. higher-dose ICS/LABA, 1002 vs. 1341µg) or doubled (17% reduction vs. higher-dose ICS alone, 554 vs. 1000µg). For most comparisons, the magnitude of reduction in exacerbations with budesonide/formoterol maintenance and reliever therapy versus comparators was similar during cold periods and non-cold periods, with wider confidence limits reflecting the shorter observation period for cold periods (2.7 weeks/patient/year); however, the magnitude of benefit for budesonide/formoterol maintenance and reliever therapy compared with higher-dose ICS was much lower during colds (17%) than non-cold periods (47%). Together, these findings suggest that the dose and/or timing of ICS are important for reducing cold-related exacerbations.

Previous evidence for the protective effect of controller treatment during clinical colds has
been largely inferred from all-cause exacerbations. Maintenance ICS reduces the risk of all-cause exacerbations by ∼50% compared with placebo, with a greater reduction for higher versus lower ICS doses [5]. Adding LABA reduces all-cause exacerbations compared with ICS alone, although the advantage of adding LABA is smaller when the comparator is double-dose ICS [5]. By contrast with the present findings, increasing ICS dose after several days of worsening asthma is ineffective [16], except perhaps with a quadrupled dose [16].

However, cold-related and non-cold-related exacerbations may respond differently to treatment. Rhinovirus infection leads to rapid induction of multiple inflammatory cytokines and chemokines, and an influx of inflammatory cells (predominantly neutrophils) into the airway [2, 3]. By contrast, exacerbations induced by ICS reduction are primarily characterised by eosinophilic inflammation [6]. Likewise, in emergency department presentations, viral exacerbations are characterised by higher sputum neutrophils, lower lung function, and a greater need for hospitalisation [4, 29], whereas non-viral exacerbations have sputum eosinophilia and better clinical outcomes [4]. In addition, cold-related exacerbations are associated with reduced diurnal variability and lack of response to SABA compared with poorly-controlled asthma [8].

Few studies in adults have examined the effect of long-term treatment on cold-related exacerbations, although several studies in infants and children have shown no reduction with regular ICS (e.g. [30]). In an experimental rhinovirus study in adults, 2 weeks’ ICS pre-treatment failed to prevent viral-induced airway inflammation [31]. In pooled clinical trials, fewer cold-related exacerbations occurred with salmeterol/fluticasone than with fluticasone alone [13]. Further insights into the differences seen in the present analyses have been obtained from in vitro studies, which have shown a dose-dependent reduction in rhinovirus-induced interleukin-6 (IL-6), IL-8, CCL5 (lymphocyte chemokine), and CXCL8 (neutrophil attractor/activator) when airway epithelial cells were pre-treated with corticosteroids [10, 11, 32]. Pre-treatment with corticosteroids also abolished rhinovirus-induced loss of β_{2}-receptor function [33]. Salmeterol enhanced rhinovirus-induced IL-6 production [11], which may contribute to adverse effects of LABA monotherapy [34], but salmeterol/fluticasone downregulated CCL5 and CXCL8 mRNA and protein at significantly lower concentrations than fluticasone alone, suggesting a synergistic effect [10]. Furthermore, rhinovirus-induced IL-8 release was mediated by oxidative stress [35], suggesting a potential mechanism for relative corticosteroid resistance when rhinovirus-induced inflammation becomes established. Together, these previous studies indicate that ICS dose during viral infection, and the inclusion of LABA, may be important in preventing or managing cold-related exacerbations.

An additional factor is that patients taking conventional fixed-dose maintenance treatment use SABA when symptoms worsen with a cold, often with no increase in anti-inflammatory treatment unless OCS are used. SABA may have pro-inflammatory effects [36-38], which are enhanced during rhinovirus infection [11], perhaps via atypical coupling, which may also reduce their bronchodilator effect [39]. Post-infection treatment of epithelial cells with budesonide and formoterol shows additive or synergistic suppression of rhinovirus-induced IL-6 and CCL5 [12]. Budesonide/formoterol maintenance and reliever therapy may provide protection not only by driving an early concurrent increase in ICS, but also by ensuring that viral-induced inflammation is not further enhanced by unopposed use of SABA [34, 40]. Given the rapid and intense inflammatory response to viral infection, further research is also needed to investigate potential action plan strategies for patients taking conventional fixed-dose maintenance ICS/LABA with as-needed SABA, for example to evaluate the effectiveness of an immediate increase in ICS dose or short burst of OCS as soon as asthma begins to worsen with a cold rather than delaying additional anti-inflammatory treatment until increased symptoms have been present for around 5 days (as in previous studies of higher-dose ICS [41, 42]) or have progressed to the extent that OCS would currently be recommended [17, 18]. Although OCS are inexpensive and effective in the
treatment of severe asthma exacerbations, concerns by the medical community [43, 44] and patients [45] about their side-effects indicate that the safety and cost-effectiveness of different action plan strategies should be evaluated in prospective studies in which all colds, cold-related exacerbations and medication side-effects are documented.

In future studies, it will be important to document the cause of asthma exacerbations rather than assume a uniform response. Detailed prospective studies are needed with nasopharyngeal and/or sputum sampling for viral identification and inflammatory characterisation. Routine use of a standardised cold questionnaire or even the simple question “Do you have a cold today?” [28] would increase our ability to identify and understand heterogeneity in asthma exacerbations and in therapeutic responses.

This retrospective study provides additional insight into strategies that may reduce the risk of cold-related asthma exacerbations, and supports the role of ICS dose and/or timing in this context. In patients with a history of previous exacerbations – a strong predictor of future exacerbations – the risk of cold-related exacerbations can be halved by using budesonide/formoterol as maintenance and reliever therapy, compared with same maintenance dose ICS/LABA with SABA as needed. There may be no significant differences in cold-related exacerbations with budesonide/formoterol maintenance and reliever therapy compared with higher-dose maintenance ICS or ICS/LABA, but the choice of regimen needs to take into account the costs and side effects of long-term, high-dose treatment and the potential risks of unopposed SABA treatment during viral infections, as well as patient preference. Prospective studies are needed to confirm the implications of these findings for management of worsening asthma during viral infections.
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Contributions

HR proposed the analysis, participated in the study design, analysis and interpretation of data, and wrote and revised the manuscript. CJ participated in the study design, analysis and interpretation of data and the writing of the manuscript. SQ participated in planning and writing of the manuscript. MRS participated in data evaluation and writing of the manuscript. EDB was involved in the study design, analysis and interpretation of data and the writing of the manuscript. PO'B contributed to the development of the research strategy, evaluation and analysis of the data, and the writing of the manuscript. MH contributed to data analysis and approved the manuscript. RB participated in the study design, analysis and interpretation of data and contributed to the final manuscript. TH contributed to the design, interpretation of results and writing of the manuscript. GB proposed the analysis and contributed to the manuscript. AT contributed to the analysis plan, analysis of the results and writing of the manuscript. US contributed to the statistical analysis plan, performed the statistical analyses, and contributed to writing of the manuscript. SP contributed to the statistical analysis plan, performed the statistical analyses, and contributed to writing of the manuscript. GSE was involved in the study design, analysis and interpretation of data and the writing of the manuscript. All authors approved the final manuscript.
References


Table 1: Demographic and baseline data

<table>
<thead>
<tr>
<th>Pooled patient data *</th>
<th>All comparators</th>
<th>BUD/FORM maintenance + reliever therapy</th>
<th>Northern hemisphere, all</th>
<th>Southern hemisphere, all</th>
<th>Tropics, all</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7281</td>
<td>5226</td>
<td>8279</td>
<td>2644</td>
<td>1584</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3030 (42)</td>
<td>2161 (41)</td>
<td>3628 (44)</td>
<td>1092 (41)</td>
<td>471 (30)</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>39.0 (4–83)</td>
<td>39.0 (4–89)</td>
<td>39.7 (4–89)</td>
<td>37.0 (5–83)</td>
<td>40.2 (12–82)</td>
</tr>
<tr>
<td>Entry ICS, µg (range)</td>
<td>709 (100–3200)</td>
<td>715 (160–2000)</td>
<td>705 (100–2400)</td>
<td>730 (200–3200)</td>
<td>714 (100–2000)</td>
</tr>
<tr>
<td>Entry LABA use, %</td>
<td>44</td>
<td>47</td>
<td>48</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Asthma diagnosis, median years (range)</td>
<td>11 (0–77)</td>
<td>11 (0–70)</td>
<td>9 (0–71)</td>
<td>16 (1–71)</td>
<td>13 (1–77)</td>
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<tr>
<td>FEV1, % predicted normal</td>
<td>72.0 (12.5)</td>
<td>71.7 (12.4)</td>
<td>72.9 (12.1)</td>
<td>71.9 (13.1)</td>
<td>66.9 (11.8)</td>
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<tr>
<td>As-needed reliever use, inhalations/day</td>
<td>2.2 (1.4)</td>
<td>2.1 (1.4)</td>
<td>2.1 (1.4)</td>
<td>2.5 (1.4)</td>
<td>2.4 (1.5)</td>
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<td>Total daily symptom score, 0–6</td>
<td>1.77 (0.96)</td>
<td>1.78 (0.94)</td>
<td>1.74 (0.96)</td>
<td>1.94 (0.92)</td>
<td>1.65 (0.96)</td>
</tr>
</tbody>
</table>

Pooled baseline and demographic data for patients receiving budesonide/formoterol maintenance and reliever therapy and pooled fixed dose maintenance treatments + SABA, and for all patients split by geographic location. Data are means (standard deviations) unless otherwise indicated.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe et al. [23] was not included in the main pooled analysis.

For demographic data for each of the different treatment groups, refer to the individual references (higher maintenance dose ICS plus SABA [21, 22]; same maintenance dose ICS/LABA plus SABA [22, 23]; higher maintenance dose ICS/LABA plus SABA [24, 25]; budesonide/formoterol maintenance and reliever

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For demographic data for each of the different treatment groups, refer to the individual references (higher maintenance dose ICS plus SABA [21, 22]; same maintenance dose ICS/LABA plus SABA [22, 23]; higher maintenance dose ICS/LABA plus SABA [24, 25]; budesonide/formoterol maintenance and reliever
therapy [21-23]). BUD/FORM, budesonide/formoterol; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; SABA, short-acting β₂-agonist.
## Table 2: Summary of reported colds and all-cause exacerbations

<table>
<thead>
<tr>
<th></th>
<th>All data*</th>
<th>Higher maintenance dose ICS + SABA</th>
<th>Same maintenance dose ICS/LABA + SABA*</th>
<th>Higher maintenance dose ICS/LABA + SABA</th>
<th>Same maintenance dose ICS/LABA + SABA or LABA†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All comparators* maintenance + reliever therapy</td>
<td>HMD ICS + SABA + reliever therapy</td>
<td>SMD ICS/LABA + SABA + reliever therapy</td>
<td>HMD ICS/LABA + SABA + reliever therapy</td>
<td>SMD ICS/LABA + SABA† + LABA† reliever therapy†</td>
</tr>
<tr>
<td>Patients, N</td>
<td>7281</td>
<td>1866</td>
<td>2044</td>
<td>3371</td>
<td>1138</td>
</tr>
<tr>
<td>Mean months of observation/patient</td>
<td>8.36</td>
<td>10.70</td>
<td>10.95</td>
<td>5.49</td>
<td>11.04</td>
</tr>
</tbody>
</table>

**All reported colds**

<table>
<thead>
<tr>
<th></th>
<th>1278 (18)</th>
<th>413 (22)</th>
<th>421 (21)</th>
<th>444 (13)</th>
<th>237 (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of events</td>
<td>1703</td>
<td>562</td>
<td>600</td>
<td>541</td>
<td>337</td>
</tr>
<tr>
<td>Event/patient/yr (95% CI)</td>
<td>0.34 (0.32–0.35)</td>
<td>0.34 (0.31–0.37)</td>
<td>0.32 (0.30–0.35)</td>
<td>0.34 (0.32–0.38)</td>
<td>0.32§ (0.29–0.36)</td>
</tr>
</tbody>
</table>

**All exacerbations**

<table>
<thead>
<tr>
<th></th>
<th>1222 (17)</th>
<th>391 (21)</th>
<th>437 (21)</th>
<th>394 (12)</th>
<th>245 (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of events</td>
<td>1904</td>
<td>643</td>
<td>707</td>
<td>554</td>
<td>377</td>
</tr>
</tbody>
</table>

All reported colds

- Patients with event, n (%): 1278 (18) 892 (17) 413 (22) 421 (21) 444 (13) 237 (21)
- Total number of events: 1703 562 600 541 337
- Event/patient/yr (95% CI): 0.34 (0.32–0.35) 0.34 (0.31–0.37) 0.32 (0.30–0.35) 0.34 (0.32–0.38) 0.32§ (0.29–0.36)

All exacerbations

- Patients with event, n (%): 1222 (17) 586 (11) 391 (21) 437 (21) 394 (12)
- Total number of events: 1904 813 643 707 554

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All exacerbations

- Patients with event, n (%): 1222 (17) 586 (11) 391 (21) 437 (21) 394 (12)
- Total number of events: 1904 813 643 707 554
### Analysis of reported colds and exacerbations for budesonide/formoterol maintenance and reliever therapy versus all pooled fixed-dose maintenance treatments + SABA and versus individual treatment arms.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe et al. [23] was not included in the main pooled analysis. † Data from the Rabe et al study only [23], including both ICS/LABA plus terbutaline (SABA) and formoterol (LABA) as-needed arms. ‡ P < 0.001 vs. comparator(s); § P < 0.05 vs. same maintenance dose ICS/LABA + LABA. # The lower rate of reported colds in this treatment arm was due to fewer adverse event reports of pharyngitis and nasopharyngitis.

<table>
<thead>
<tr>
<th>Event/patient/yr</th>
<th>0.38 (0.36–0.39)</th>
<th>0.38 (0.35–0.41)</th>
<th>0.35 (0.32–0.38)</th>
<th>0.36 (0.33–0.40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(0.20–0.23)</td>
<td>(0.19–0.23)</td>
<td>(0.22–0.28)</td>
<td>(0.25–0.31)</td>
</tr>
</tbody>
</table>

For further information on definitions of higher and same maintenance dose, refer to Table E1 of the online supplement. BUD/FORM, budesonide/formoterol; HMD, higher maintenance dose; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; SABA, short-acting β2-agonist; SMD, same maintenance dose.
Table 3: Exacerbation rates and treatment comparisons by cold status

<table>
<thead>
<tr>
<th></th>
<th>Mean ICS dose (μg/day, BDP equiv)</th>
<th>Exacerbation rate or ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cold periods*</td>
<td>Non-cold periods</td>
</tr>
<tr>
<td><strong>Pooled dataset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy</td>
<td>727</td>
<td>2.00 (1.59–2.53)</td>
</tr>
<tr>
<td>All fixed-dose maintenance treatments + SABA</td>
<td>987</td>
<td>3.15 (2.66–3.74)</td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy vs. all fixed-dose maintenance treatments + SABA</td>
<td></td>
<td>0.64 (0.48–0.84); P = 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.57 (0.51–0.64); P &lt; 0.001</td>
</tr>
<tr>
<td><strong>BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS + SABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy</td>
<td>554</td>
<td>1.93 (1.30–2.86)</td>
</tr>
<tr>
<td>Higher maintenance dose ICS + SABA</td>
<td>1000</td>
<td>2.32 (1.62–3.33)</td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy vs. comparator</td>
<td></td>
<td>0.83 (0.49–1.40); P = 0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.53 (0.44–0.64); P &lt; 0.001</td>
</tr>
<tr>
<td><strong>BUD/FORM maintenance and reliever therapy vs. same maintenance dose ICS/LABA + SABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy</td>
<td>582</td>
<td>1.99 (1.41–2.80)</td>
</tr>
<tr>
<td>Same maintenance dose ICS/LABA + SABA</td>
<td>389</td>
<td>4.17 (3.23–5.38)</td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy vs. comparator</td>
<td></td>
<td>0.48 (0.31–0.72); P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50 (0.42–0.61); P &lt; 0.001</td>
</tr>
<tr>
<td><strong>BUD/FORM maintenance and reliever therapy vs. higher maintenance dose ICS/LABA + SABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy</td>
<td>1002</td>
<td>2.34 (1.60–3.41)</td>
</tr>
<tr>
<td>Higher maintenance dose ICS/LABA + SABA</td>
<td>1341</td>
<td>3.25 (2.42–4.36)</td>
</tr>
<tr>
<td>BUD/FORM maintenance + reliever therapy vs. comparator</td>
<td></td>
<td>0.72 (0.45–1.15); P = 0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.70 (0.57–0.86); P &lt; 0.001</td>
</tr>
</tbody>
</table>

The table shows the annualised exacerbation rate (exacerbations/year) and the rate ratio for exacerbations for budesonide/formoterol maintenance and reliever therapy versus comparator(s) by cold status (cold period/non-cold period) using the statistical analysis model (see Methods). A cold period was defined as the 14 days following onset of a reported cold. Cold periods comprised an average of 2.7 weeks of the treatment period per patient. Mean ICS dose was calculated as BDP-CFC equivalent, based on GINA guidelines [17], over the whole randomised treatment period, including ICS delivered in maintenance and, where relevant, reliever therapy.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe et al. [23] was not included in
the main pooled analysis but a comparison of the three different relievers is shown in online Table E5.

BDP, CFC-beclomethasone dipropionate; BUD/FORM, budesonide/formoterol; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; SABA, short-acting β₂-agonist.
Figure Legends and Footnotes

Figure 1: Reported colds, all-cause exacerbations, allergic rhinitis/conjunctivitis and non-infectious adverse events in northern and southern hemispheres, by month and by season

Annualised incidence (events/patient/year) of A) reported colds B) exacerbations C) non-infectious adverse events and D) allergic rhinitis or conjunctivitis, in all studies (budesonide/formoterol maintenance and reliever therapy vs. pooled fixed-dose maintenance treatments + SABA) for northern and southern hemispheres (left), and by seasonal month (right). Seasonal months: southern hemisphere 1 = January to 12 = December; northern hemisphere 1 = July to 12 = June. The ICS/LABA plus formoterol as-needed arm in the study by Rabe et al. [23] was not included in these pooled analyses. AE, adverse event; BUD/FORM, budesonide/formoterol; SABA, short-acting β₂-agonist.
Figure 2: Time from onset of first reported cold to first severe asthma exacerbation

For patients reporting a cold, the figure shows Kaplan–Meier plots of time from cold index day (onset of first reported cold) to first severe asthma exacerbation for budesonide/formoterol maintenance and reliever therapy vs.: A) pooled fixed-dose maintenance treatments + SABA*; B) higher maintenance dose ICS + SABA; C) same maintenance dose ICS/LABA + SABA*; D) higher maintenance dose
ICS/LABA + SABA. Only the first 14 days are shown.

* The ICS/LABA plus formoterol as-needed arm in the study by Rabe et al. [23] was not included in these pooled analyses; data from all three arms of that study are shown in Figure 3.

BUD/FORM, budesonide/formoterol; CI, confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; SABA, short-acting β₂-agonist.

Figure 3: Time from first onset of cold to first severe asthma exacerbation comparing budesonide/formoterol maintenance and reliever therapy with budesonide/formoterol plus LABA or SABA as needed

BUD/FORM maintenance and reliever therapy vs.:

BUD/FORM + terbutaline (SABA) as needed HR 0.31; 95% CI: 0.16–0.60; \( P < 0.001 \)

BUD/FORM + formoterol (LABA) as needed HR 0.38; 95% CI: 0.19–0.76; \( P = 0.0066 \)

BUD/FORM + formoterol (LABA) as needed vs.:

BUD/FORM + terbutaline (SABA) as needed HR 0.81; 95% CI: 0.49–1.33; \( P = 0.41 \)

For patients reporting any cold in the study by Rabe et al. [23], the figure shows a Kaplan–Meier plot of time from cold index day (onset of first reported cold) to first severe asthma exacerbation for...
budesonide/formoterol maintenance and reliever therapy vs. same maintenance dose ICS/LABA (BUD/FORM) plus SABA (terbutaline) or plus LABA (formoterol). Only the first 14 days are shown. BUD/FORM, budesonide/formoterol; LABA, long-acting $\beta_2$-agonist; SABA, short-acting $\beta_2$-agonist.

Figure 4: Reliever use associated with first reported cold
For patients reporting a cold, the figure shows mean total daily reliever use (inhalations/patient/24 hours) over days –7 to 21 from the onset of first reported cold, from all studies, for all comparators pooled (A and B) and for budesonide/formoterol maintenance and reliever therapy (C and D). Panels B and D are for patients experiencing a severe exacerbation during the cold period. The dotted line indicates the on-treatment mean across the whole study for the same groups of patients. BUD/FORM, budesonide/formoterol.