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Original article

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Please cite this article as: Hatter L, Bruce P, Braithwaite I, *et al*. ICS-formoterol reliever *versus* ICS and SABA reliever in asthma: a systematic review and meta-analysis. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00701-2020).

ICS-formoterol reliever vs ICS and SABA reliever in asthma: a systematic review and meta-analysis

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Word count: 3177

Summary take home message: As-needed low-dose ICS-formoterol prolongs the time to first severe asthma exacerbation compared to maintenance ICS plus SABA reliever, and represents a therapeutic alternative for patients, particularly if severe exacerbation prevention is the primary aim of treatment.

ABSTRACT

Background: The Global Initiative for Asthma recommends as-needed inhaled corticosteroid (ICS)-formoterol as an alternative to maintenance ICS plus short-acting $beta_2$-agonist (SABA) reliever at Step 2 of their stepwise treatment algorithm. Our aim was to assess the efficacy and safety of these two treatment regimens, with a focus on severe exacerbation prevention.

Methods: We performed a systematic review and meta-analysis of all randomised controlled trials (RCTs) comparing as-needed ICS-formoterol with maintenance ICS plus SABA. MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from database inception to 12 December 2019. The primary outcome was time to first severe exacerbation. RCTs were excluded if they used as-needed budesonide-formoterol as part of a maintenance and reliever regimen, or did not report on severe exacerbations. The review is registered with PROSPERO (CRD42020154680).

Results: Four RCTs (n=8065 participants) were included in the analysis. As-needed ICS-formoterol was associated with a prolonged time to first severe exacerbation (hazard ratio 0.85, 95%CI 0.73 to 1.00; p=0.048) and reduced daily ICS dose (mean difference -177.3mcg, 95%CI -182.2 to -172.4). Asthma symptom control was worse in the as-needed group (ACQ-5 mean difference 0.12, 95%CI 0.09 to 0.14), though did not meet the minimal clinically important difference of 0.50 units. There was no significant difference in serious adverse events (odds ratio 1.07 95%CI 0.84 to 1.36).

Conclusion: As-needed ICS-formoterol offers a therapeutic alternative to maintenance low-dose ICS plus SABA in asthma and may be the preferred option if severe exacerbation prevention is the primary aim of treatment.

INTRODUCTION

The Global Initiative for Asthma (GINA) recommends inhaled corticosteroid (ICS)-formoterol as the preferred reliever across the spectrum of asthma severity in adults and adolescents [1]. At Step 1 of the GINA stepwise treatment algorithm, this recommendation is supported by data from two randomised controlled trials (RCTs), which demonstrated as-needed combination low-dose budesonide-formoterol reduced the risk of severe exacerbations by at least 60% compared to short-acting $beta_2$-agonist (SABA) reliever therapy in mild asthma [2, 3]. At Steps 3 and 4, this recommendation is supported by evidence that in patients taking maintenance ICS with a long-acting $beta_2$-agonist (LABA), the use of ICS-formoterol reliever rather than SABA reliever reduced the risk of severe exacerbations by 32% [4]. At Steps 4 and 5, this recommendation is supported by evidence that in patients taking budesonide-formoterol maintenance and reliever therapy, the risk of a severe exacerbation is reduced by 23% compared with maintenance ICS-LABA at double the equivalent ICS dose, plus SABA reliever [4].

The one step where GINA suggests equipoise between treatments is at Step 2, with low-dose as-needed ICS-formoterol now recommended as an alternative to maintenance low-dose ICS plus SABA reliever [1]. This update was first made in 2019 following publication of two large double-blind RCTs, which demonstrated non-inferiority for severe exacerbations between the two regimens [2, 5, 6, 7]. Two real-world RCTs have since reported that as-needed budesonide-formoterol reduced the risk of a severe exacerbation compared with maintenance budesonide plus SABA reliever in patients with mild to moderate asthma [3, 8].

Undertaking a systematic review to identify additional studies and combining all available results in a summary data meta-analysis has the potential to improve the precision of the estimates of the treatment effects for the comparison between these two regimens. The aim was to compare the efficacy and safety of as-needed budesonide-formoterol with maintenance ICS plus SABA reliever in adults and children with mild to moderate asthma. The primary focus was on severe exacerbation prevention as an important clinical and public health outcome [9], and in recognition of the zero-tolerance approach to severe exacerbations that has been advocated [10].

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis is registered with PROSPERO (CRD42020154680) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11]. Two reviewers (LH and PB) searched MEDLINE (Ovid), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from database inception to 12 December 2019. Full search strategies can be found in the supplementary appendix (figure S1). Results were enhanced through forward-backward citation tracking of relevant publications.

RCTs comparing as-needed ICS-formoterol with maintenance ICS plus SABA reliever in adults and/or children with mild to moderate asthma were eligible for inclusion. RCTs were excluded if they used as-needed budesonide-formoterol as part of a maintenance and reliever regimen, or did not report on severe exacerbations. Non-RCTs and studies without full-text publications were also excluded. No language restrictions were built into our literature search.

Two reviewers (LH and PB) independently screened the titles, abstracts, and full-text publications against the eligibility criteria. Full-text publications that met the inclusion criteria were included in the meta-analysis. Disagreements were resolved through discussion within the review team.

Data analysis

The primary outcome was time to first severe exacerbation. Secondary outcomes included: rate ratio (RR) of severe exacerbation; risk of at least one severe exacerbation, Emergency Department (ED) visit, hospital admission, combined ED visit or hospital admission, serious adverse events (SAE), and death; mean daily ICS dose; asthma control questionnaire (ACQ-5) scores; and Forced Expiratory Volume over one second (FEV_1). Mean number of daily formoterol-adjusted $beta_2$-agonist actuations was a post-hoc outcome variable.

Data on the primary and secondary outcomes were extracted into tables (tables S3 to S7). This was done independently by three reviewers (LH, PB, and RB). Missing data relevant to the meta-analysis were obtained from study authors on request. All data were cross-checked and verified by the same three reviewers prior to inclusion in the meta-analysis.

Three reviewers (JF, LH and PB) independently assessed risk of bias using the Cochrane Collaboration Risk of Bias tool for RCTs [12].

Inverse variance weighted meta-analysis was used for the hazard ratio (HR) for time to first severe exacerbation, the rate ratio of number of severe exacerbations, the odds ratio (OR) for risk of at least one severe exacerbation, odds ratio for risk of at least one SAE, mean difference for investigational product ICS dose, mean difference in the number of $beta_2$-agonist actuations, ACQ-5, and FEV_1. Peto's method (Peto's odds ratio [POR]) was used for estimation of the risk of at least one ED visit, hospital admission, ED visit or hospital admission, and death.

The meta-analyses of the hazard ratios for time to first severe exacerbation, and the rate ratios for number of severe exacerbations, used the logarithm-transformed estimates of hazard and rate and their confidence intervals to estimate the variance, on the logarithm scale, for the estimates. The variances were estimated by dividing the difference between the upper and lower confidence bounds by 3.92, and squaring the results. Back-transformation by exponentiation gives estimates back on the scale of rate ratios and hazard ratios. The risk of at least one exacerbation, SAE, ED visit,

hospitalisation, combined ED visit or hospitalisation, and death used the reported counts of events and non-events. For ICS dose, the reported counts, mean, and standard deviation by study arm were used. For the $beta_2$-agonist actuations, the mean and standard deviation by study arm were used, with the data standardized in formoterol equivalents, based on actuations equivalent to formoterol at a dose of 6mcg having bronchodilator bioequivalence with terbutaline at a dose of 500mcg and salbutamol at 200mcg, when administered repeatedly in acute severe asthma [13, 14, 15]. For ACQ-5 and FEV_1 the study estimates of mean differences and confidence intervals were used. The variances were estimated by the difference between the upper and lower confidence bounds, divided by 3.92, and squared. Homogeneity statistics were calculated for each analysis as well as an estimate of the I-squared (I^2) statistic. Fixed-effects pooled estimates were calculated. Meta-analyses were performed using SAS version 9.4.

Certainty of evidence for each outcome was assessed independently by two reviewers (LH and PB) using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias (figure S2).

RESULTS

The literature search yielded 1947 results (figure 1). Following removal of duplicates, 1540 references were screened against the eligibility criteria, of which 1536 were excluded. Four RCTs (8065 participants) comparing as-needed budesonide-formoterol (4023 participants) with maintenance ICS plus SABA reliever (4042 participants) in adults (n=4) and adolescents aged 12 years and older (n=2) were included in the meta-analysis (table 1) [2, 3, 5, 8]. No studies examined the use of as-needed ICS-formoterol in children aged 11 years and under. All studies compared as-needed budesonide-formoterol via dry-powder inhaler (DPI) with maintenance budesonide DPI plus SABA reliever (either salbutamol pressurised metered-dose inhaler [pMDI] [8] or terbutaline DPI) [2, 3, 5].

Key differences between the studies (tables 1 and S1) included the larger size and double-blind, placebo-controlled design of the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 studies. [2, 5]. By comparison the PeRsonalised Asthma Combination Therapy with an Inhaled Corticosteroid And fast-onset Long acting beta agonist (PRACTICAL) and the Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) trials were smaller and used an open-label, real-world design [3, 8]. In all four studies, participants were receiving Step 1 [2, 3, 5, 8] or 2 [2, 5, 8] treatment at study entry, although some participants enrolled in PRACTICAL were on Step 3 therapy at baseline. PRACTICAL was the only fully independently funded study.

All studies were deemed to be at low risk of bias (figure S3).

As-needed budesonide-formoterol was associated with a prolonged time to first severe exacerbation (HR 0.85, 95% CI 0.73 to 1.00, p=0.048; table 2 and figure 2).

As-needed budesonide-formoterol reduced the rate ratio of severe exacerbations (RR 0.85, 95% CI 0.72 to 1.00; figure 3A) and the risk of at least one severe exacerbation (OR 0.86, 95% CI 0.73 to 1.01; figure 3B). Quantitative heterogeneity was evident in these analyses with the two larger studies showing less of a difference between the two treatment groups.

There were fewer ED visits in the as-needed budesonide-formoterol group (POR 0.65, 95% CI 0.43 to 0.98). There was no difference in hospitalisations (POR 0.85, 95% CI 0.49 to 1.49), or the combination of ED visits or hospitalisations (POR 0.73, 0.52 to 1.04; figure 4). The data sets contributing to these variables had few, or no, events.

There was no difference between the two groups in the number of participants experiencing at least one SAE (OR 1.07 95% CI 0.84 to 1.36) or deaths (POR 0.52, 95% CI 0.10 to 2.57). Of the six reported deaths, one was asthma-related and occurred in the maintenance ICS group.

The ICS dose taken was lower in the as-needed budesonide-formoterol group across all four studies (mean difference -177.3mcg, 95% CI -182.2 to -172.4), with evidence of heterogeneity (I^2 98.8).

The number of formoterol-adjusted $beta_2$-agonist-containing actuations per day was higher in the as-needed budesonide-formoterol group across all four studies (mean difference 0.08, 95% CI 0.05 to 0.10), with evidence of heterogeneity (I^2 94.2).

The ACQ-5 score was higher in the as-needed budesonide-formoterol group (mean difference 0.12, 95% CI 0.09 to 0.14). The FEV_1 was lower in the as-needed budesonide-formoterol group (mean difference -27.4mL, 95% CI -40.7 to -14.1). There was evidence of heterogeneity (I^2 74.8) with the two SYGMA studies having a larger and negative effect on FEV_1, favouring ICS maintenance.

DISCUSSION

This meta-analysis has shown modest evidence of a statistically significant 15% reduction in the hazard ratio for a first severe exacerbation with as-needed budesonide-formoterol compared with maintenance budesonide plus SABA reliever in adults and adolescents with mild to moderate asthma. We propose that this difference is clinically important, although acknowledge there is no agreed standard for what constitutes a minimal clinically importance difference (MCID) in exacerbation risk. Similar estimates of a 15% reduction in the rate ratio of severe exacerbations and a 14% reduction in the risk of at least one severe exacerbation were noted, together with a 35% reduction in risk of at least one ED visit. In contrast, the maintenance ICS regimen was associated with a greater level of asthma symptom control and higher lung function, although the differences were well below the MCID for these measures [16, 17].

The primary outcome of time to first severe exacerbation was chosen as it minimises the effect of changes to the randomised treatment (such as the introduction of additional medication) and participant withdrawal [9, 18], which occurred in the Novel START study following a first severe exacerbation. Severe exacerbation was similarly defined in all studies, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria [9]. The Novel START study definition included the “prescription” of oral corticosteroids, whereas the other studies measured “use”. It is unlikely this difference would affect the validity of the meta-analysis, based on the assumption that the ratios of severe exacerbations do not depend on individual definitions.

There was evidence of heterogeneity in the findings for the primary outcome variable between the four RCTs. Much of this can be explained by the difference in study designs, with the results of the two open-label studies having a greater treatment effect (favouring as-needed budesonide-formoterol) than the two large double-blind studies. By removing the need to take a placebo inhaler every day, the open-label design allowed the use of budesonide-formoterol as a single medication with no requirement for a regular inhaler. This enabled patient behaviour to be closer to that seen in real life and may enhance the generalizability of these findings to clinical practice.

A number of secondary outcomes that showed no evidence of a significant difference between the two groups, such as the number of deaths and hospital admissions, were limited by the small number of events. However, the significant 35% reduction in ED visits with as-needed budesonide-formoterol suggests this regimen may provide protection against the most severe exacerbations associated with greater mortality risk [19].

A reduction in the daily dose of ICS was observed in the as-needed budesonide-formoterol group in all four studies. Although there was evidence of heterogeneity in this analysis, the estimates for all four studies were in the same direction. This supports the idea that timing of ICS administration, driven by symptom-directed bronchodilator use, may be of greater importance for preventing severe exacerbations than total ICS dose received. The ability of participants taking as-needed budesonide-formoterol to increase their dose in response to worsening symptoms may lead to resolution of an exacerbation before it becomes severe. Conversely, participants on maintenance ICS are restricted to fixed twice-daily dosing, which may result in under-dosing of ICS during exacerbations, and a greater dose than is required during periods of excellent symptom control. Patient unease over unnecessary medication use was highlighted in a sub-study of 306 participants enrolled in the PRACTICAL trial, in which 47% of participants believed there was no need to take a preventer inhaler every day when well, and 40% were concerned about taking too much medication [20].

Mean adherence to prescribed maintenance ICS in the four studies was considerably higher than in clinical practice (56% to 79% vs less than 50%, respectively) [21, 22]. This was likely due in part to the motivational influence of electronic inhaler monitors and frequent study visits on participant behaviour (Hawthorne effect) [23], which occurred in both the double-blind and open-label trials. As

adherence influences outcomes, it is possible that the efficacy of maintenance ICS was greater in the trials than might be expected in clinical practice.

$Beta_2$-agonist use is also relevant to the comparative clinical efficacy of the two regimens. In all four studies, participants taking as-needed budesonide-formoterol required a greater number of formoterol-adjusted $beta_2$-agonist actuations per day than participants using a SABA reliever. Although reliever use was low in both groups, and the mean difference of 0.08 per day was small, it is likely that a component of the increased efficacy of budesonide-formoterol reliever compared with SABA may be due to the greater bronchodilator dose of formoterol. When added to ICS-LABA maintenance therapy, formoterol reduces the rate of severe exacerbations by 22% compared with terbutaline at similar bronchodilator doses [24].

The mean ACQ-5 score was 0.12 units lower with maintenance ICS across the four studies, indicating better symptom control. This difference is likely due to the intrinsic characteristic of as-needed therapy, in which inhaler use is largely symptom-driven. Of note, participants in the double-blind studies were only permitted to use their as-needed medications for symptom relief, whereas prophylactic use was allowed in the open-label studies. An important clinical consideration is that the 0.12 unit difference in the ACQ-5 score was below the MCID of 0.50 units [16]. A related point is that the inclusion of subjects with mild asthma means there is likely to be a floor effect, as it would be difficult for those with well-controlled asthma at baseline to achieve the required 0.50 unit change. It is therefore probable that although the magnitude of the overall difference is not clinically important, for some people the use of maintenance ICS will result in a clinically important improvement in symptom control.

FEV_1 was measured differently in the double-blind (pre-bronchodilator FEV_1) and open-label (on-treatment FEV_1) studies, which may account for some of the heterogeneity in this analysis. The FEV_1 was higher in the maintenance ICS group in all four studies, with a mean difference of -27.4mL, which is below the MCID of 230mL [17].

Fractional exhaled nitric oxide (FeNO), a biomarker of type-2 airway inflammation, was only measured in the two open-label studies [3, 8] and not included in the meta-analysis. In steroid-naive participants, a reduction in FeNO was observed with as-needed budesonide-formoterol, providing evidence of an anti-inflammatory effect of ICS when taken on a purely as needed basis. A greater benefit was observed with maintenance ICS although the magnitude of the difference was of uncertain clinical importance [25]. This data was derived from one-year studies, and the longer-term effects of these regimens on airways inflammation will be important to determine.

It is worthwhile considering the results of this meta-analysis in line with the GINA 2020 report, which reconfirms ICS-formoterol as a therapeutic alternative to maintenance ICS plus SABA at Step 2. When deciding between the two treatments, GINA ascribes particular importance to preventing

severe exacerbations and minimising the need for daily ICS [1]. Our findings suggest as-needed ICS-formoterol is superior on both counts.

A separate consideration is to whom these results apply. The observation that in all four studies the mean ACQ did not meet the cut point for well-controlled asthma (<0.75 units) [26] at the end of 12 months treatment with maintenance budesonide, suggests that a substantial proportion would have met the GINA criteria for moderate asthma [1, 27]. The findings may therefore be generalizable to both patients with mild and moderate asthma.

There are several limitations to this review. First, multiple related outcomes were analysed in order to provide a comprehensive assessment of severe exacerbations. It was considered that this would be more informative than an individual measure of severe exacerbation, however Type 1 error may be an issue, particularly for outcomes where event counts were sparse and confidence intervals wide. Second, a study by Lazarinis and colleagues was excluded as it did not report on severe exacerbations, risking selection bias for some of the secondary outcomes [28]. Any potential bias would likely be minimal due to the short duration of the study (six weeks) and the small number of participants included (44 participants). Third, it is unclear if these results are applicable to other ICS-fast-onset beta$_2$-agonist (both ICS-SABA and ICS-fast-onset LABA) combinations; further studies of alternative anti-inflammatory relievers are needed. Fourth, the findings in this meta-analysis are only relevant to adults and adolescents due to the absence of evidence in children aged 11 years and younger. Trials of ICS-SABA reliever combinations in children suggest possible efficacy of as-needed ICS-formoterol in this age group [29, 30], and there is a clear need for RCTs to confirm this [31, 32, 33]. Fifth, based on the current data from one-year studies, it is not possible to determine the long-term effects of the as-needed ICS-formoterol regimen, including on lung function. Sixth, economic evaluation of the treatment regimens was beyond the scope of this review, but is necessary to guide practical implementation.

To conclude, this systematic review and meta-analysis provides evidence of moderate certainty that as-needed budesonide-formoterol prolonged the time to first severe exacerbation in adults and adolescents with mild and moderate asthma compared with maintenance low-dose ICS plus SABA reliever. These findings support the GINA 2020 recommendation that as-needed ICS-formoterol is a therapeutic alternative to maintenance ICS at Step 2 particularly if severe exacerbation prevention is the primary aim of treatment. This analysis also complements the evidence that as-needed ICS-formoterol reduces severe exacerbation risk when taken alone in mild asthma, or together with maintenance ICS-formoterol in more severe asthma, and is the preferred reliever across the spectrum of asthma severity.

Acknowledgements

We would like to thank Michael Fauchelle of the Wellington Medical and Health Sciences Library, University of Otago, for his help designing the literature search strategy. We would also like to thank the SYGMA, Novel START and PRACTICAL study teams for providing additional data relevant to this analysis. IB, MH, JF, MW, and RB are all named authors on the Novel START and PRACTICAL studies.

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Table 1: Characteristics of included studies

Study	Design	Duration	Sites	Population	No. of participants (intervention vs control)*	Primary outcome (analysis)	Intervention	Control
SYGMA 1 O'Byrne et al. 2018	RCT, parallel-group, double-blind placebo-controlled	52 weeks	261 sites, 18 countries	Adults and adolescents (≥12 years)	2559 (1277 vs 1282)	Mean percentage of electronically recorded weeks with well-controlled asthma per patient (non-inferiority)†	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed plus twice daily placebo	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500mcg (Turbuhaler) as-needed
SYGMA 2 Bateman et al. 2018	RCT, parallel-group, double-blind placebo-controlled	52 weeks	350 sites, 25 countries	Adults and adolescents (≥12 years)	4176 (2089 vs 2087)	Annualised rate of severe exacerbations (non-inferiority)‡	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed plus twice daily placebo	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500mcg (Turbuhaler) as-needed
Novel START Beasley et al. 2019	RCT, parallel-group, open-label, real-world	52 weeks	16 sites, 4 countries	Adults (≥18 years)	425 (220 vs 225)	Annualised rate of asthma exacerbations (superiority)	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus Albuterol 100mcg (Ventolin pMDI) two inhalations as-needed
PRACTICAL Hardy et al. 2019	RCT, parallel-group, open-label, real-world	52 weeks	15 sites, 1 country	Adults and adolescents (≥18 years)	885 (437 vs 448)	Number of severe exacerbations per patient per year (superiority)	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 250mcg (Bricanyl

								Turbuhaler, AstraZeneca) two inhalations as-needed

Abbreviations: pMDI, pressurised Metered-Dose Inhaler; RCT, Randomised Controlled Trial.
*Intervention refers to as-needed budesonide formoterol, control refers to maintenance budesonide plus SABA reliever. Participant numbers refer to as-needed ICS-formoterol and maintenance ICS plus SABA arms only; numbers for SABA only arms in SYGMA 1 and Novel START not included.
† Superiority analysis for as-needed budesonide-formoterol vs short-acting beta$_2$-agonist (primary), and non-inferiority analysis for as-needed budesonide-formoterol vs maintenance budesonide plus short-acting beta$_2$-agonist (secondary).
‡Initially superiority
This table does not include details of additional trial arms, which were present in the SYGMA 1 and Novel START studies. All information derived from published trial protocols (including trial registries), manuscripts and supplementary material.

Table 2: Summary of findings and certainty of evidence

Outcomes	Studies	Budesonide-Formoterol		Maintenance Budesonide		Pooled Fixed Effect (95% CI)	I-squared (95% CI)	Certainty of evidence
		Event (n)	Participants (n)	Event (n)	Participants (n)			
Severe asthma exacerbations								
Time to first severe exacerbation	2,3,5,8	294	4023	342	4042	HR 0.85 (0.73 to 1.00)	60.7 (0.0 to 86.9)	Moderate
Number of severe exacerbations	2,3,5,8	351	4023	399	4042	RR 0.85 (95% CI 0.72 to 1.00)	49.5 (0 to 83.3)	Moderate
Risk of at least one severe exacerbation	2,3,5,8	294	4023	342	4042	OR 0.86 (0.73 to 1.01)	53.5 (0 to 84.6)	Moderate
ED visits with systemic glucocorticoid use	2,3,5,8	39	4023	60	4042	POR 0.65 (0.43 to 0.98)	0.0 (0 to 76.1)	Moderate
Hospital admissions	2,3,5,8	26	4023	27	4042	POR 0.85 (0.49 to 1.49)	0.0 (0.0 to 89.1)	Low
ED visit or Hospital admissions	2,3,5,8	62	4023	80	4042	POR 0.73 (0.52 to 1.04)	0.0 (0 to 82.7)	Moderate
Serious adverse events								
Risk of at least one SAE	2,3,5,8	140	4028	131	4042	OR 1.07 (0.84 to 1.36)	30.1 (0 to 74.6)	Very Low
Deaths	2,3,5,8	2	4028	4	4042	POR 0.52 (0.10 to 2.57)	0.0 (0 to 84.5)	Very Low
Inhaled medication use								
ICS dose	2,3,5,8	NA	3641	NA	3649	MD -177.3 (-182.2 to -172.4)	98.8 (98.2 to 99.2)	Moderate
B_2-Agonist daily actuations[*]	2,3,5,8	NA	3640	NA	3645	MD 0.08 (0.05 to 0.10)	94.2 (88.8 to 97.2)	Low
Asthma symptom control and lung function[†]								
ACQ-5 score	2,3,5,8	NA	4023	NA	4042	MD 0.12 (0.09 to 0.14)	42.5 (0 to 80.7)	High

FEV_1‡	2,3,5,8	NA	4023	NA	4042	MD -27.4 (-40.7 to -14.1)	74.8 (29.9 to 90.9)	Low

Abbreviations: ACQ-5, Asthma Control Questionnaire; CI, Confidence Interval; ED, Emergency Department; FEV_1, Forced Expiratory Volume over one second; HR, Hazard Ratio; ICS, Inhaled Corticosteroid; MD, Mean Difference; OR, Odds Ratio; POR, Peto Odds Ratio; RR, Rate Ratio; SAE, Serious Adverse Event.

* For the meta-analysis, daily $beta_2$-agonist-containing actuations were standardized to formoterol 6mcg = salbutamol 200mcg = terbutaline 500mcg. Data for daily $beta_2$-agonist-containing actuations from the SYGMA 1 and SYGMA 2 studies were provided by the study authors, on request.

† No. of participants in ACQ-5 and FEV_1 represents total number of participants in each arm; it is not possible to determine exact numbers as individual analyses used mixed linear models to measure continuous and repeated measures.

‡ SYGMA 1 and SYGMA 2 reported pre-bronchodilator FEV_1 measurements; Novel-START and PRACTICAL reported on-treatment FEV_1 measurements.

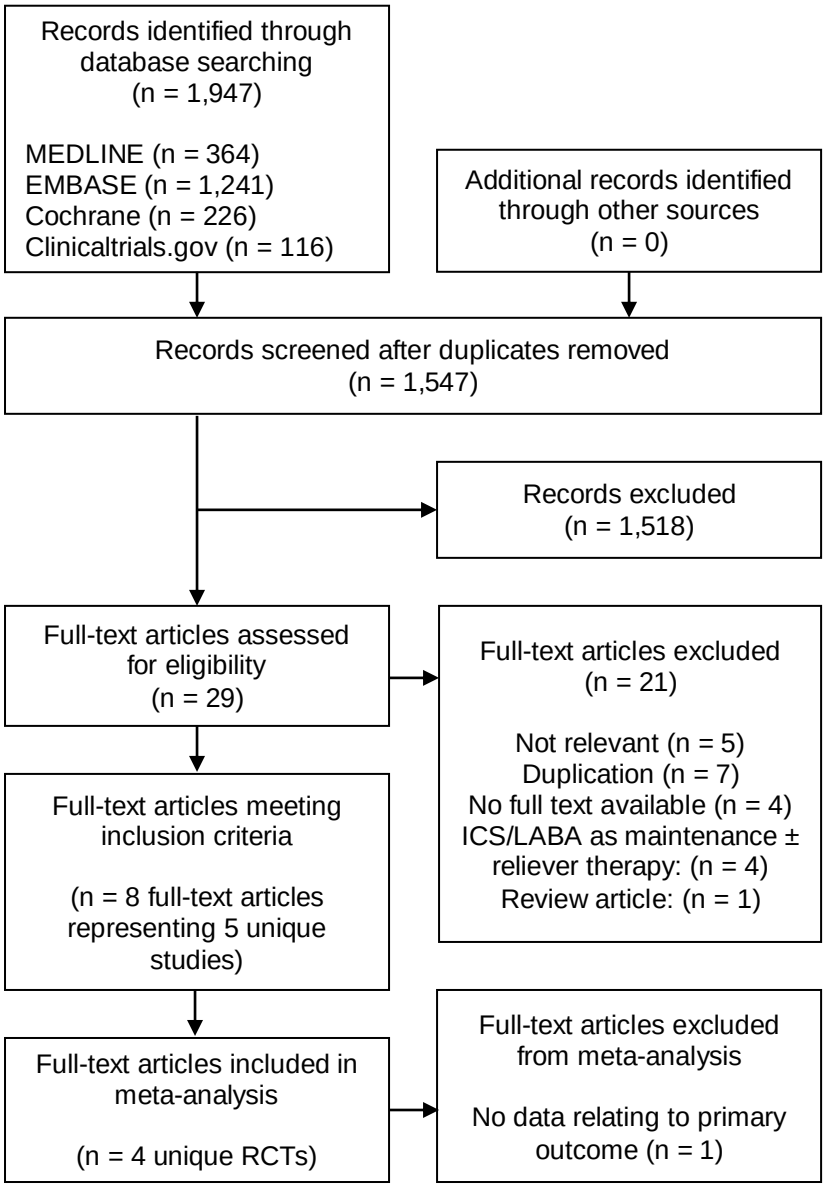
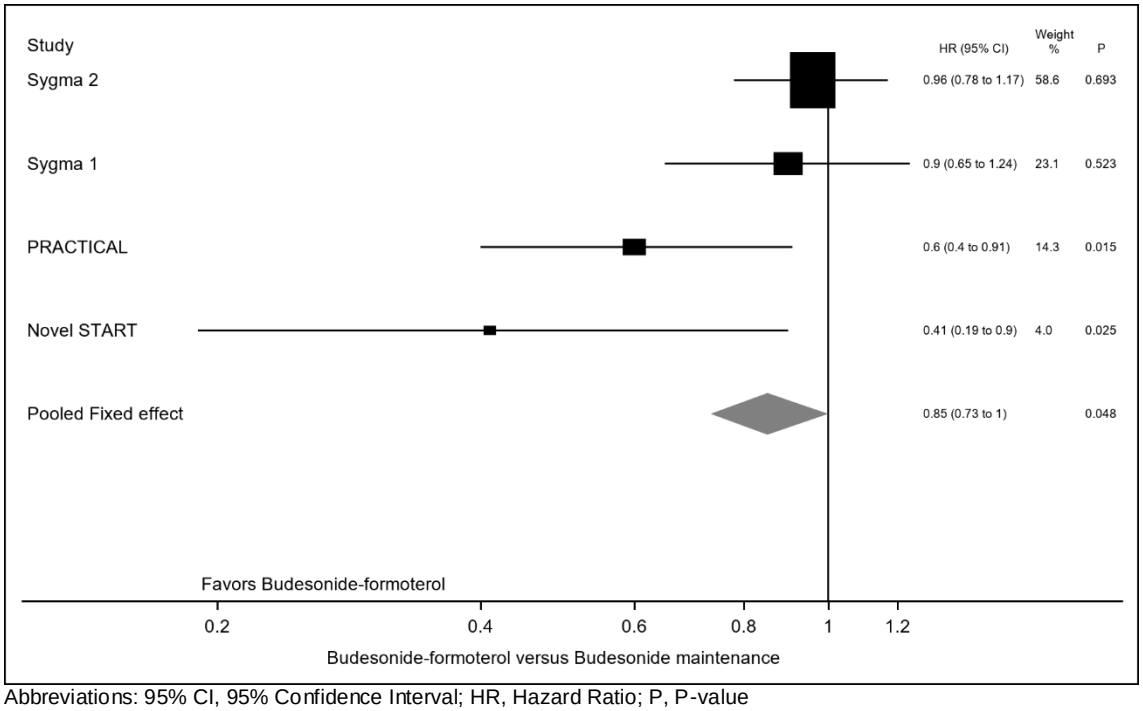
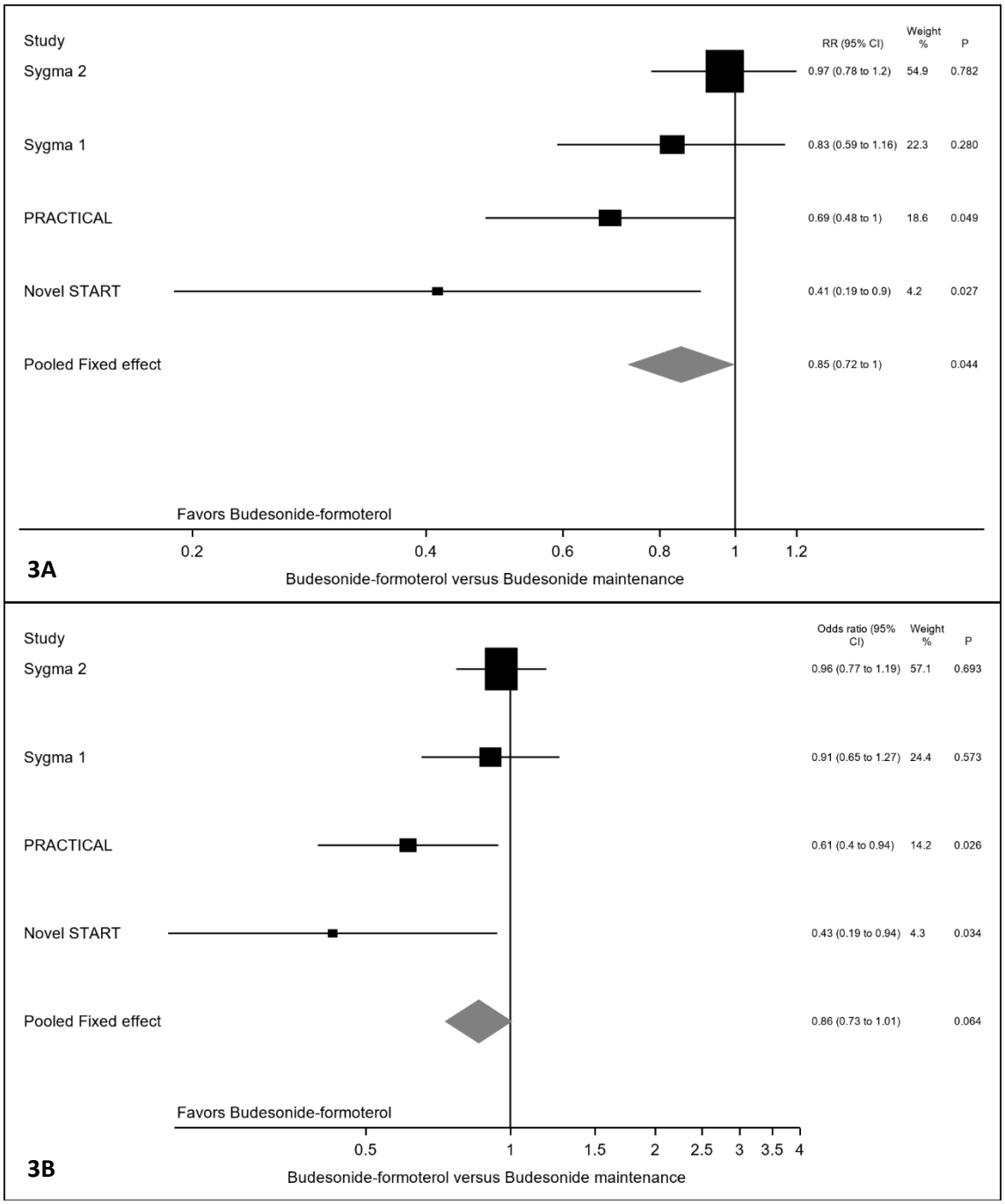

Records identified through database searching (n = 1,947)
MEDLINE (n = 364)
EMBASE (n = 1,241)
Cochrane (n = 226)
Clinicaltrials.gov (n = 116)
Additional records identified through other sources (n = 0)
Records screened after duplicates removed (n = 1,547)
Records excluded (n = 1,518)
Full-text articles assessed for eligibility (n = 29)
Full-text articles excluded (n = 21)
Not relevant (n = 5)
Duplication (n = 7)
No full text available (n = 4)
ICS/LABA as maintenance ± reliever therapy: (n = 4)
Review article: (n = 1)
Full-text articles meeting inclusion criteria
(n = 8 full-text articles representing 5 unique studies)
Full-text articles included in meta-analysis
(n = 4 unique RCTs)
Full-text articles excluded from meta-analysis
No data relating to primary outcome (n = 1)

Figure 2: Pooled fixed effect for the hazard ratio of time to first severe exacerbation



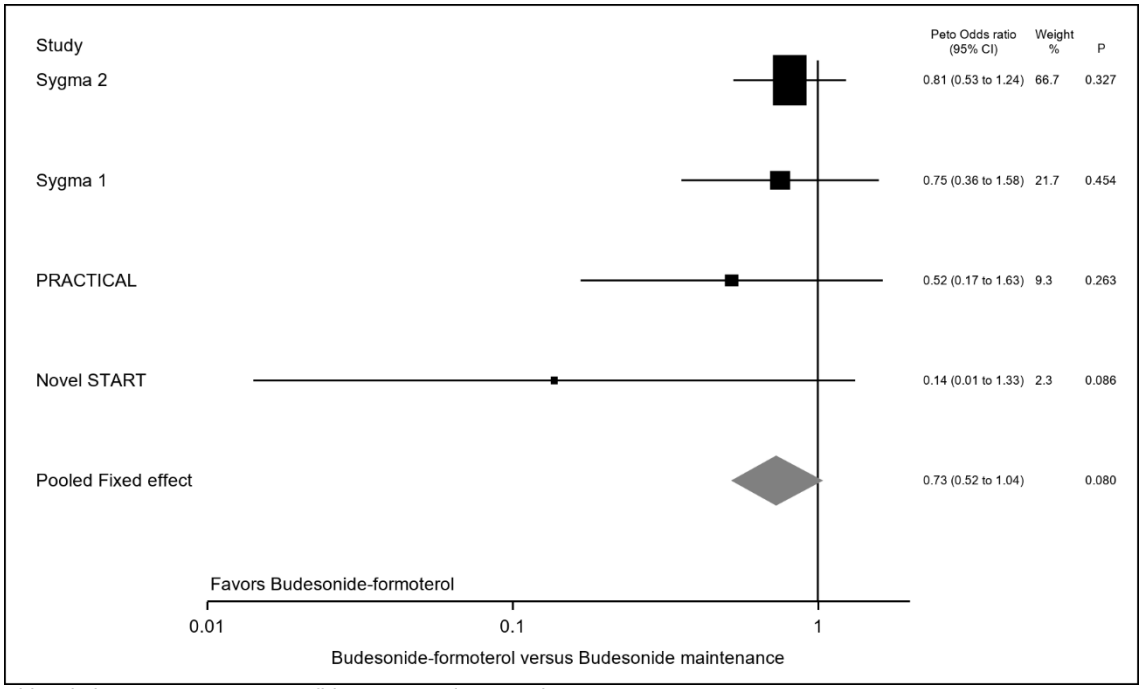
Abbreviations: 95% CI, 95% Confidence Interval; HR, Hazard Ratio; P, P-value

FIGURE 3: Pooled fixed effect of A) rate ratio of severe exacerbations, and B) odds ratio for relative risk of severe exacerbations



Abbreviations: 95% CI, 95% Confidence Interval; RR, Rate Ratio; P, P-value

FIGURE 4: Pooled fixed effect of the combination of ED visits or hospitalisations



Abbreviations: 95% CI, 95% Confidence Interval; P, P-value

Supplementary Online Content

Contents

Figure S1: Literature Search Strategies

Search strategies were developed with the assistance of a librarian. The filter employed is a modified version of the Highly Sensitive Search Strategy (HSSS) filter by Cochrane (Cochrane handbook 5.1, chapter 6.4.11.1) [1], incorporating an element of the Royle and Waugh Brief RCT Search Strategy (BRSS) [2], and the P3 filter developed by Cooper *et al*.[3]

Search strategy for MEDLINE (Ovid Interface):

Line	Search	Hits
1	Budesonide/	4341
2	Formoterol Fumarate/	1640
3	1 and 2	506
4	Budesonide, Formoterol Fumarate Drug Combination/	146
5	((budesonide adj3 formoterol) or symbicort or duoresp or fobumix or vannair).mp.	758
6	or/3-5	872
7	asthma/ or asthma, aspirin-induced/ or asthma, exercise-induced/ or asthma, occupational/ or status asthmaticus/	125127
8	(asthma* or wheez*).mp.	179820
9	7 or 8	179820
10	6 and 9	639
11	limit 10 to (clinical trial, phase iii or clinical trial or controlled clinical trial or multicenter study or randomized controlled trial)	241
12	(controlled clinical trial or randomized controlled trial).pt.	583372
13	random*.ab.	1060065
14	placebo.ab.	203130
15	clinical trials as topic/ or randomized controlled trials as topic/	313999
16	clinical trial/ or exp randomized controlled trial/	800055
17	trial.ti.	208826
18	clinical trial, phase iii/	15919
19	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.	64471
20	or/12-19	1772717
21	10 and 20	355
22	11 or 21	364

Search strategy for EMBASE (Ovid interface):

ID	Search term(s)	Hits
1	budesonide/	20239
2	formoterol/	5809
3	formoterol fumarate/	1024
4	1 and (2 or 3)	2410
5	budesonide plus formoterol/	2416
6	((budesonide and formoterol) or symbicort or duoresp or fobumix or vannair).mp.	4531
7	or/4-6	4531
8	asthma/ or allergic asthma/ or aspirin exacerbated respiratory disease/ or asthmatic state/ or exercise induced asthma/ or experimental asthma/ or extrinsic asthma/ or intrinsic asthma/ or mild intermittent asthma/ or mild persistent asthma/ or moderate persistent asthma/ or nocturnal asthma/ or occupational asthma/ or severe persistent asthma/	249875
9	(asthma* or wheez*).mp.	295789
10	8 or 9	296008
11	7 and 10	3205
12	limit 11 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 3 clinical trial)	913
13	random*.ab.	1438759
14	placebo.ab.	288866
15	"clinical trial (topic)"/ or "randomized controlled trial (topic)"/	268080
16	clinical trial/ or exp randomized controlled trial/	1249073
17	trial.ti.	283879
18	phase 3 clinical trial/	44175
19	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.	115870
20	or/13-19	2499949
21	11 and 20	1216
22	12 or 21	1241

Search strategy for the Cochrane Central Register of Controlled Trials:

ID	Search	Hits
1	MeSH descriptor: [Budesonide] this term only	1674
2	MeSH descriptor: [Formoterol Fumarate] this term only	925
3	#1 AND #2	319
4	MeSH descriptor: [Budesonide, Formoterol Fumarate Drug Combination] this term only	149
5	((budesonide adj3 formoterol) or symbicort or symbiocort or duoresp or fobumix or vannair):ti,ab,kw	399
6	#3 OR #4 OR #5	639
7	MeSH descriptor: [Asthma] explode all trees	11093
8	(asthma* or wheez*):ti,ab,kw	33977
9	#7 OR #8	33977
10	#3 AND #9	226

Search strategy for ClinicalTrials.gov:

Condition or disease: Asthma
Other terms: Product containing budesonide and formoterol
Study type: Interventional studies (clinical trials)
Study results: All studies
Results: 116

Terms	Search Results*	Entire Database**
Synonyms		
product containing budesonide and formoterol	104 studies	191 studies
symbicort	100 studies	183 studies
formoterol and budesonide	4 studies	6 studies
budesonide-formoterol	3 studies	8 studies
Budesonide and formoterol product	1 studies	1 studies
product containing budesonide	112 studies	539 studies
budesonide	112 studies	534 studies
Pulmicort	13 studies	106 studies
Budecort	--	3 studies
Butacort	--	1 studies
Eltair	--	1 studies
entocort	--	16 studies
Nasocort	--	1 studies
Preferid	--	1 studies
Rhinocort	--	15 studies
Uceris	--	2 studies
formoterol	114 studies	505 studies
foradil	5 studies	50 studies
oxis	5 studies	17 studies
arformoterol	--	18 studies
Brovana	--	19 studies
oxeze	--	2 studies
Perforomist	--	6 studies
budesonide	112 studies	539 studies
Pulmicort	13 studies	106 studies
Budecort	--	3 studies
Butacort	--	1 studies
Eltair	--	1 studies
entocort	--	16 studies
Nasocort	--	1 studies
Preferid	--	1 studies
Rhinocort	--	15 studies
Uceris	--	2 studies
containing	9 studies	20,902 studies
contains	4 studies	6,161 studies
contain	2 studies	2,829 studies
contained	2 studies	1,352 studies
Comprise	1 studies	1,015 studies
product	26 studies	18,640 studies
asthma	116 studies	3,644 studies
Asthmatic	27 studies	537 studies

Figure S2: Certainty of Evidence

Certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) handbook and GRADEpro software [4, 5].

Risk of bias: Risk of bias for each outcome was assessed using the Cochrane Risk of Bias assessment tool (Appendix B). The contributed weight of the study to the meta-analysis was also considered. The certainty of evidence was downgraded for outcomes with serious or very serious risk of bias.

Imprecision: Imprecision refers to the degree of certainty around the best estimate of the absolute effect. The number of events, width of confidence intervals (narrow <0.10, moderate 0.10 to 0.50, wide >0.50), whether the confidence intervals included the possibility of small or no effect, and estimated Optimal Information Size (set with alpha 0.05 and power 0.8), were all used to determine whether the certainty of evidence for each outcome should be downgraded.

Inconsistency: Inconsistency refers to the degree of uniformity in the direction and magnitude of effects(s) across all studies. I^2 was reviewed in line with the Cochrane criteria (Cochrane handbook 5.1, chapter 10.10.2) [1]:

0% to 40%: might not be important;
30% to 60%: may represent moderate heterogeneity;
50% to 90%: may represent substantial heterogeneity;
75% to 100%: considerable heterogeneity.

Outcome trends per study were examined on forest plots. Study designs were reviewed for cause of inconsistency. Outcomes were downgraded if there was evidence of serious or very serious inconsistency.

Indirectness: Indirectness relates to whether the evidence answers the research question posed. Population, intervention, control, direct comparison, and outcomes were assessed. Certainty of evidence was downgraded for serious or very serious indirectness.

Publication bias: Publication bias was assessed and certainty of evidence downgraded if there was evidence of serious or very serious reporting bias or publication bias.

Base on the above assessment, the authors ascribed one of the four certainties to each outcome:

High: The true effect is similar to the estimated effect.

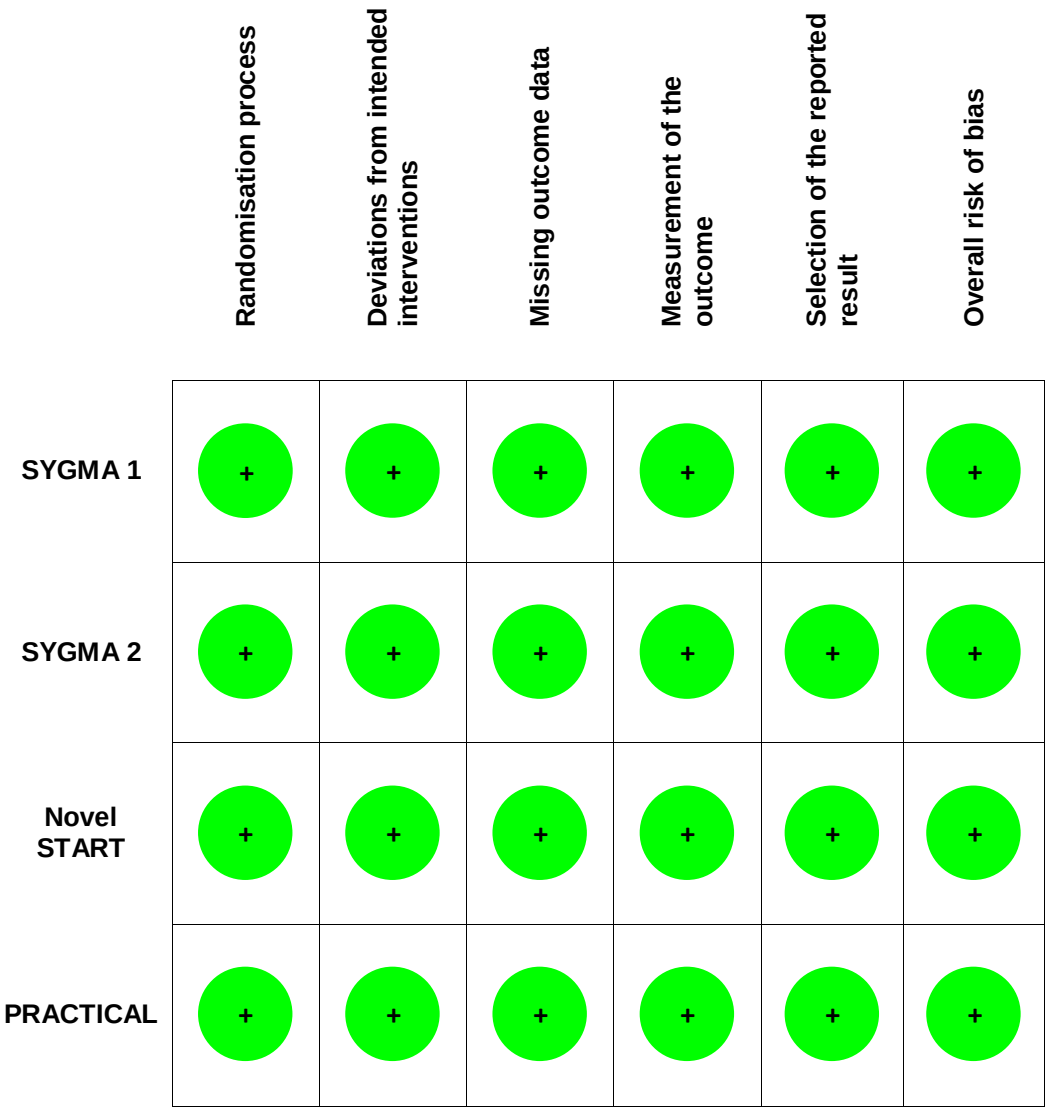
Moderate: The true effect is probably close to the estimated effect.

Low: The true effect might be markedly different from the estimated effect.

Very low: The true effect is probably markedly different from the estimated effect.

Figure S3: Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Collaboration risk of bias tool for RCTs [6].



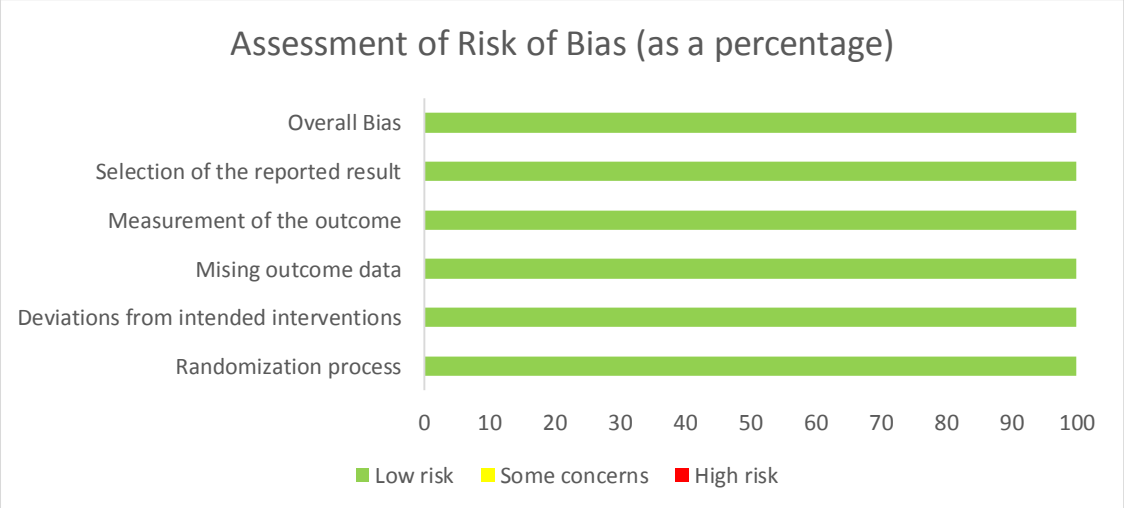


Table S1: Additional Study Characteristics

Characteristics	**SYGMA 1** [7, 8, 9]	**SYGMA 2** [7, 10, 11]	**Novel START** [12, 13, 14]	**PRACTICAL** [15, 16, 17]
Study registration	NCT02149199	NCT02224157	ACTRN12615000999538	ACTRN12616000377437
Participants, total - no.	3836	4176	648	885
Primary outcome, variable	Mean percentage of electronically recorded weeks with well-controlled asthma per patient	Annualized rate of severe exacerbations	Annualized rate of asthma exacerbations	Number of severe exacerbations per patient per year
Primary outcome, analysis	Superiority (with non-inferiority as secondary outcome)	Non-inferiority	Superiority	Superiority
Key inclusion criteria	1. Diagnosis of asthma according to GINA criteria, ≥6 month history; 2. Require GINA step 2 treatment; 3. FEV1: Pre-bronchodilator ≥60% predicted, post-bronchodilator ≥80% predicted, with reversibility; 4. Use of SABA ≥3 separate days in last week of run-in period.	1. Diagnosis of asthma according to GINA criteria, ≥6 month history; 2. Require GINA step 2 treatment; 3. FEV1: Pre-bronchodilator ≥60% predicted, post-bronchodilator ≥80% predicted, with reversibility; 4. Use of SABA ≥3 separate days in last week of run-in period.	1. Doctor diagnosis of asthma; 2. Use of SABA as sole therapy in preceding 3 months; 3. Use of SABA on ≥2 occasions, but ≤2 occasions per day, in the previous 4 weeks.	1. Doctor diagnosis of asthma; 2. Use of SABA with or without maintenance ICS (≤800µg budesonide equivalent) in the previous 12 weeks.
Key exclusion criteria	1. Smoking: ≥10 pack years; 2. History of life-threatening asthma; 3. Any significant disease or disorder which may put the patient at risk or influence the study results.	1. Smoking: ≥10 pack years; 2. History of life-threatening asthma; 3. Any significant disease or disorder which may put the patient at risk or influence the study results.	1. Use of non-SABA asthma medication in preceding 3 months; 2. Unstable asthma in 6 weeks prior to study (including use of oral steroids); 3. Diagnosis of other lung disease; 4. Smoking ≥20 pack years (or ≥10 with onset of respiratory symptoms after the age of 40 years).	1. Use of Non-ICS or SABA medication in preceding 3 months; 2. Unstable asthma in 6 weeks prior to study (including use of oral steroids); 3. Diagnosis of other lung disease; 4. Smoking ≥20 pack years (or ≥10 with onset of respiratory symptoms after the age of 40 years).

Characteristics	**SYGMA 1** [7, 8, 9]	**SYGMA 2** [7, 10, 11]	**Novel START** [12, 13, 14]	**PRACTICAL** [15, 16, 17]
Definition of severe exacerbation	Use of systemic corticosteroids for ≥3 days, or a hospitalization or ED visit because of asthma, requiring systemic corticosteroids	Use of systemic corticosteroids for ≥3 days, or a hospitalization or ED visit because of asthma, requiring systemic corticosteroids	Prescription of systemic corticosteroids for ≥3 days, or a hospitalization or ED visit because of asthma, requiring systemic corticosteroids	Use of systemic corticosteroids for ≥3 days, or a hospitalization or ED visit because of asthma, requiring systemic corticosteroids
Withdrawal of participants following a severe exacerbation	No	No	Yes	No
Run-in period, duration - weeks	2 to 4	2 to 4	N/A	N/A
Run-in period, medication	Terbutaline 500mcg as-needed only	Terbutaline 500mcg as-needed only	N/A	N/A
Treatment arm: as-needed ICS-formoterol	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed plus twice daily placebo	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed plus twice daily placebo	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide-formoterol 200/6mcg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed
Treatment arm: maintenance ICS plus SABA reliever	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500mcg (Bricanyl Turbuhaler, AstraZeneca) as-needed	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500mcg (Bricanyl Turbuhaler, AstraZeneca) as-needed	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus Albuterol 100mcg (Ventolin pMDI, GlaxoSmithKline) two inhalations as-needed	Budesonide 200mcg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 250mcg (Bricanyl Turbuhaler, AstraZeneca) two inhalations as-needed
Treatment arm: SABA only	Terbutaline 500mcg (Bricanyl Turbuhaler) as-needed	NA	Albuterol 100mcg (Ventolin pMDI) two inhalations as-needed	NA
Funding source(s)	AstraZeneca	AstraZeneca	AstraZeneca and New Zealand Health Research Council	New Zealand Health Research Council

Abbreviations: ED, Emergency Department; ICS, Inhaled Corticosteroid; FEV_1, Forced Expiratory Volume over 1 second; SABA, Short-acting $beta_2$-agonist
All information derived from published trial protocols (including trial registries), manuscripts and supplementary material.

Table S2: Participant Baseline Demographics and Clinical Characteristics

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	220	225	437	448
Age, years								
Mean (range)	39.8 (12 to 80)	39.0 (12 to 85)	41.3 (12 to 83)	40.7 (12 to 83)	36 (18 to 74.4)	34.9 (18.3 to 74.1)	43.3 (18.3 to 74.7)	42.8 (18.1 to 75.8)
12 to <18 – no. (%)	161 (12.6)	173 (13.5)	205 (9.8)	206 (9.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥18 (%) – no. (%)	1116 (87.4)	1109 (86.5)	1884 (90.2)	1881 (90.1)	220 (100.0)	225 (100.0)	437 (100.0)	448 (100.0)
Female – no. (%)	777 (60.8)	797 (62.2)	1308 (62.6)	1289 (61.8)	122 (55.5)	129 (57.3)	244 (56)	241 (54)
Ethnicity – no. (%)								
White / European	721 (56.5)	728 (56.8)	1408 (67.4)	1406 (67.4)	168 (76.4)	171 (76.0)	342 (78.3)	357 (79.7)
Asian	340 (26.6)	347 (27.1)	399 (19.1)	403 (19.3)	14 (6.4)	25 (11.1)	29 (6.6)	34 (7.6)
Other, incl. Black, Māori or Pacific	216 (16.9)	207 (16.1)	282 (13.5)	278 (13.3)	38 (17.3)	29 (12.9)	66 (15.1)	57 (12.7)
Smoking status - no. (%)								
Current	34 (2.7)	30 (2.3)	53 (2.5)	54 (2.6)	18 (8.2)	22 (9.8)	39 (9)	24 (5)
Ex-Smoker	139 (10.9)	120 (9.4)	266 (12.7)	283 (13.6)	56 (25.5)	40 (17.8)	123 (28)	112 (25)
Never	1104 (86.5)	1132 (88.3)	1770 (84.7)	1750 (83.9)	146 (66.4)	163 (72.4)	275 (63)	312 (70)
Asthma medication – no. (%)								
SABA only	565 (44.2)	576 (44.9)	959 (45.9)	975 (46.7)	220 (100.0)	225 (100.0)	132 (30.2)	132 (29.5)
ICS or LTRA plus SABA	712 (55.8)	706 (55.1)	1130 (54.1)	1112 (53.3)	0 (0.0)	0 (0.0)	305 (69.8)	316 (70.5)
Severe exacerbations, prev. 12mths – no. (%)	257 (20.1)	241 (18.8)	459 (22)	460 (22)	12 (5.5)	17 (7.6)	53 (12)	52 (12)
ACQ-5 score – mean (SD)	1.6 (1.0)	1.6 (1.0)	1.5 (0.9)	1.5 (0.9)	1.1 (0.7)	1.1 (0.7)	1.1 (0.8)	1.2 (0.8)
FEV_1 (SD)*								
Mean, L	2.9 (0.8)	2.9 (0.8)	3.0 (0.8)	3.0 (0.8)	3.3 (0.9)	3.3 (0.9)	3.0 (0.9)	3.0 (0.9)

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
Percentage predicted value – mean	95.9 (14.0)	95.7 (13.4)	96.3 (13.8)	96.0 (13.5)	89.8 (14.1)	90.3 (13.6)	87.8 (16.4)	87.4 (16.3)
FeNO - ppb								
Mean (SD)	NA	NA	NA	NA	50.8 (46.1)	54.3 (44.0)	39.0 (33.9)	47.1 (44.8)
Median (IQR)	NA	NA	NA	NA	37.0 (18.0 to 66.0)	38.0 (20.0 to 76.0)	26.0 (15.0 to 51.0)	30.0 (18.0 to 62.5)
Range	NA	NA	NA	NA	3.0 to 300.0	5.0 to 200.0	5.0 to 222.0	5.0 to 300 .0

Abbreviations: ACQ-5, Asthma Control Questionnaire; FEV1, Forced Expiratory Volume over one second; LTRA, Leukotriene Receptor Antagonists; SD, standard deviation.

*SYGMA 1 and SYGMA 2 reported pre-bronchodilator FEV1 measurements; Novel-START and PRACTICAL reported on-treatment FEV1 measurements.

All data as published in study manuscripts and supplementary material.

Table S3: Severe Exacerbations

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	220	225	437	448
Severe exacerbations (n)	**(1277)**	**(1282)**	**(2089)**	**(2087)**	**(220)**	**(225)**	**(437)**	**(448)**
Total no.	77	89	217	221	9	21	48	68
Patients with ≥1	71	78	177	184	9	21	37	59
Time to first (HR)	0.90 (95% CI 0.65 to 1.24)		0.96 (95% CI 0.78 to 1.17)		0.41 (95% CI 0.19 to 0.90)		0.60 (95% CI 0.40 to 0.91)	
Annualised rate	0.07	0.09	0.11	0.12	0.05	0.12	0.12	0.17
Rate ratio	0.83 (95% CI 0.59 to 1.16)		0.97 (95% CI 0.78 to 1.20)		0.41 (95% CI 0.19 to 0.90)		0.69 (95% CI 0.48 to 1.00)	
ED visits and Hospitalisations (n)	**(1277)**	**(1282)**	**(2089)**	**(2087)**	**(220)**	**(225)**	**(437)**	**(448)**
ED visits (with SCS) – ≥1 visit	7	10	25	36	0	3	4	7
ED visits (with SCS) – total no.	8	10	26	40	0	3	5	7
Hospital admissions – ≥1 admission	6	8	17	17	0	0	0	2
Hospital admissions – total no.	6	8	20	17	0	0	0	2
ED or hospital admissions – ≥1*	12	16	39	48	0	3	4	8
ED or Hospital admissions – total no.*	13	16	44	52	0	3	5	9

Abbreviations: ED, Emergency Department (for asthma, requiring the use of systemic corticosteroids); HR, Hazard Ratio; SCS, systemic corticosteroids.
*Data for combined ED visits or hospitalisation were provided by the SYGMA study authors, on request.

Table S4: Serious Adverse Events

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	222	225	440	448
Patients with ≥1 SAE	38	37	66	73	11	6	25	15
Events – total no.	**49**	**47**	**80**	**87**	**16**	**7**	**28**	**18**
Cardiac disorders	2	4	4	5	0	0	6	1
Congenital, familial and genetic disorders	0	0	0	0	0	0	0	1
Ear and labyrinth disorders	0	0	0	1	0	0	0	0
Eye disorders	0	0	3	1	0	0	0	0
Endocrine disorders	0	2	0	0	0	0	0	0
Eye disorders	1	1	0	0	0	0	0	0
Gastrointestinal disorders	7	4	1	3	2	0	4	1
General disorders and administration site conditions	0	0	0	0	0	0	1	0
Hepatobiliary disorders	1	2	1	6	0	0	0	1
Immune system disorders	1	0	0	2	0	0	0	0
Infections and infestations	10	11	11	14	2	2	6	2
Injury, poisoning and procedural complications	4	3	14	13	1	0	2	5
Metabolism and nutrition disorders	0	0	0	1	4	0	0	0
Musculoskeletal and connective tissue disorders	1	1	4	4	0	1	1	1

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6	1	4	4	1	0	3	1
Nervous system disorders	3	2	3	5	0	0	0	2
Product Issues	0	1	0	0	0	0	0	0
Psychiatric disorders	0	0	1	0	4	2	0	0
Renal and urinary disorders	1	2	1	1	0	0	1	0
Reproductive system and breast disorders	3	1	2	6	2	0	2	1
Respiratory, thoracic and mediastinal disorders	7	10	25	18	0	1	1	2
Skin and subcutaneous tissue disorders	1	1	2	0	0	0	0	0
Surgical and medical procedures	0	0	0	0	0	0	1	0
Vascular disorders	1	1	4	3	0	1	0	0

Abbreviations: SAE, Serious adverse events.
Terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All data as published in study manuscripts, supplementary material, and trial registries.

Table S5: Deaths

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	222	225	440	448
Events – total no.	**0**	**2**	**1**	**1**	**1**	**1**	**0**	**0**
Brain Neoplasm	0	1	0	0	0	0	0	0
Upper gastrointestinal haemorrhage	0	1	0	0	0	0	0	0
Cardiorespiratory arrest	0	0	1	0	0	0	0	0
Acute asthma exacerbation	0	0	0	1*	0	0	0	0
Suicide	0	0	0	0	0	1	0	0
Road traffic incident	0	0	0	0	1	0	0	0

All data as published in study manuscripts and supplementary material. *Asthma-related death

Table S6: Inhaled Medication Use

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	220	225	437	448
Daily dose of IP ICS (n)	**(1277)**	**(1282)**	**(2089)**	**(2087)**	**(220)**	**(225)**	**(55)**	**(55)**
Mean - no. (SD)	92.9 (102.2)	314.9 (89.2)	103.5 (109.3)	250.6 (117.6)	107 (109)	222 (113)	176 (143)	302.5 (84.8)
Median (IQR / 95% CI)*	56.9 (50.0 to 64.6)	339.8 (332.1 to 346.7)	65.6 (60.8 to 71.7)	267.2 (256.5 to 272.0)	73.1 (30.7 to 146.3)	247 (132.0 to 314.0)	164.3 (74.0 to 251.7)	328.3 (245.8 to 364)
Range	0 to 721	0 to 701	0 to 753	0 to 743	0 to 790.2	0 to 402	6.7 to 682.5	26.8 to 458.1
Adherence – mean percentage dose taken	79	79	64	63	NA	56	NA	76
Daily beta$_2$-agonist-containing actuations (n)[¥]	**(1276)**	**(1281)**	**(2089)**	**(2084)**	**(220)**	**(225)**	**(55)**	**(55)**
Mean (SD)	0.47 (0.51)	0.40 (0.56)	0.52 (0.55)	0.49 (0.70)	0.53 (0.54)	0.52 (1.03)	0.9 (0.7)	0.5 (0.6)
Median (IQR)	0.29 (0.07 to 0.72)	0.16 (0.04 to 0.52)	0.33 (0.09 to 0.79)	0.21 (0.05 to 0.65)	0.37 (0.15 to 0.73)	0.18 (0.06 to 0.46)	0.8 (0.4 to 1.3)	0.3 (0.1 to 0.6)
Min to max	0.0 to 3.6	0.0 to 3.7	0.0 to 3.8	0.0 to 7.2	0 to 3.95	0.0 to 8.7	0.0 to 3.4	0.0 to 2.7

Abbreviations: 95$ CI, 95% Confidence Interval; ICS, Inhaled Corticosteroid; IP, Investigational Product; IQR, Interquartile range; SD, standard deviation.
*95% Confidence Intervals reported in SYGMA 1 and SYGMA 2 publications; Interquartile Range reported in Novel START and PRACTICAL publications.
[¥]For analysis, formoterol 6mcg = salbutamol 200mcg = terbutaline 500mcg. Data for daily beta2-agonist-containing actuations from the SYGMA 1 and SYGMA 2 studies were provided by the study authors, on request.
All other data as reported in study manuscripts and supplementary material.

Table S7: Asthma Control and Lung Function

	SYGMA 1 [7, 8, 9]		**SYGMA 2** [7, 10, 11]		**Novel START** [12, 13, 14]		**PRACTICAL** [15, 16, 17]	
	Budesonide-Formoterol	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**	**Budesonide-Formoterol**	**Maintenance Budesonide**
No. in treatment arm	1277	1282	2089	2087	220	225	437	448
ACQ-5 - mean difference	0.149 (95% CI 0.101 to 0.198)		0.11 (95% CI 0.07 to 0.15)		0.14 (95% CI, 0.05 to 0.23)		0.06, 95% (CI -0.005 to 0.12)	
FEV1* - mean difference	-54.3mL (95% CI -78.8 to -29.8)		-32.6mL (95% CI -53.7 to -11.4)		0.004L (95% CI -0.03 to 0.04)		0.006L (-0.026 to 0.04)	

Abbreviations: ACQ-5, Asthma Control Questionnaire; FEV1, Forced Expiratory Volume over one second.
All data from published manuscripts and supplementary material. Published calculations used mixed linear models for continuous and repeated measures.

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