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Asthma control with ICS-formoterol reliever versus maintenance ICS and SABA reliever therapy: a post hoc analysis of two randomised controlled trials

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ABSTRACT

Background In randomised controlled trials, as-needed inhaled corticosteroid (ICS)-formoterol reliever therapy reduces severe exacerbation risk compared with maintenance ICS plus short-acting beta$_2$-agonist (SABA) reliever in adolescent and adult asthma, but results in slightly worse control of asthma symptoms, as measured by mean Asthma Control Questionnaire-5 (ACQ-5) score.

Objective To assess the levels and changes in asthma control for as-needed budesonide–formoterol versus maintenance budesonide plus SABA in post hoc analyses from the Novel START and PRACTICAL clinical trials.

Methods The number and proportion of participants at study end in each ACQ-5 category ('well-controlled', 'partly controlled' or 'inadequately controlled' symptoms), and in each responder category based on the minimal clinically important difference for ACQ-5 of 0.5 (improved, no change and worse) with as-needed budesonide–formoterol and maintenance budesonide plus SABA treatment were calculated.

Results With last observation carried forwards, 189/214 (88.3%) and 354/434 (81.6%) of patients in the budesonide–formoterol group had 'well-controlled' or 'partly controlled' symptoms at the end of the study, vs 183/214 (85.5%) and 358/431 (83.1%) in the budesonide maintenance group, for Novel START and PRACTICAL, respectively. The proportion of patients whose symptom control was either improved or unchanged from baseline was 190/214 (88.8%) and 368/434 (84.8%) for budesonide–formoterol, vs 185/214 (86.4%) and 376/431 (87.2%) for maintenance budesonide, in Novel START and PRACTICAL respectively.

Conclusions There were no clinically important differences in the proportions of patients with 'well-controlled' or 'partly controlled' asthma symptoms, or proportions who improved or maintained their level of control, with as-needed budesonide–formoterol versus maintenance budesonide plus SABA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the context of randomised controlled trials, asthma symptom control (measured using the Asthma Control Questionnaire-5) is worse with as-needed inhaled corticosteroid (ICS)-formoterol when compared with maintenance ICS plus short-acting beta2-agonist (SABA) therapy although the difference is well short of the minimal clinically important difference. It is not clear whether the proportion of patients who met established minimal clinically important cut points for levels of asthma symptom control, or the proportion who achieved a clinically important change in asthma symptom control, differs between the two groups.

WHAT THIS STUDY ADDS

⇒ These post hoc analyses of the Novel START and PRACTICAL studies have shown that there were no clinically important differences in the proportions with good asthma symptom control, or proportions with an improvement in asthma symptom control, between as-needed budesonide–formoterol and maintenance budesonide plus SABA treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings support the interpretation that the small differences in mean asthma symptom control between as-needed budesonide–formoterol and maintenance budesonide plus as-needed SABA seen in randomised controlled trials are unlikely to translate to clinically important differences when treatment is used in routine clinical practice.

INTRODUCTION

In mild asthma, budesonide–formoterol reliever therapy alone reduces the risk of severe exacerbations compared with short-acting beta$_2$-agonist (SABA) reliever therapy by at least 60% in adolescents and adults with asthma.[1 2] This evidence has contributed to the Global Initiative for Asthma (GINA) recommendation that SABA

should not be used as sole treatment in asthma, and that inhaled corticosteroid (ICS)-formoterol is preferred as reliever therapy to SABA reliever across the range of asthma severity.[3]

GINA also recommends that as-needed ICS-formoterol alone is the preferred therapeutic approach compared with maintenance ICS plus SABA reliever for patients with mild asthma,[3] having benefit in terms of reducing severe exacerbation risk, with a lower mean ICS dose and reduced systemic corticosteroid burden.[4 5] The ICS-formoterol reliever alone regimen is preferred by the most patients compared with a maintenance ICS based regimen, being simpler to use without the requirement for two inhalers, or to take regular scheduled daily treatment.[6–8] It also has no risk of inadvertent SABA-only treatment in those non-adherent to maintenance ICS therapy.

However, in a meta-analysis of four randomised controlled trials, asthma symptom control was worse with as-needed ICS-formoterol when compared with maintenance ICS plus SABA therapy, with a mean difference in symptom control measured by the Asthma Control Questionnaire-5 (ACQ-5) of 0.12, with 95% CIs of 0.09 to 0.14.[4] While this mean difference and the upper limit of the 95% CIs are well short of the minimal clinically important difference (MCID) of 0.50,[9] it is a finding deserving of further investigation in the two trials for which individual patient data were available.

Two key questions are whether the proportion of patients who met established cut points for levels of asthma symptom control is different, and whether the proportion who achieved a change in asthma symptom control above the MCID differs, following long-term (12 months) treatment with as-needed ICS-formoterol compared with maintenance ICS plus as-needed SABA. In this report, we present such post hoc analyses from the open-label pragmatic Novel START[1] and PRACTICAL[10] studies, and discuss the implications of the findings in the decision making for treatment of mild asthma.

METHODS

The methods and results for the Novel START and PRACTICAL studies are reported in detail elsewhere.[1 10] Novel START study was a 52-week, randomised, open-label, parallel-group, controlled trial involving adults with mild asthma. Patients were randomly assigned to one of three treatment groups: salbutamol (100 µg, two inhalations from a pressurised metered dose inhaler as needed for asthma symptoms; salbutamol group); budesonide (200 µg, one inhalation via a Turbuhaler two times per day plus as-needed salbutamol; budesonide maintenance group); or budesonide–formoterol (200 µg of budesonide and 6 µg of formoterol, one inhalation via a Turbuhaler as needed; budesonide–formoterol group). The primary outcome was the annualised rate of asthma exacerbations.

The PRACTICAL study was a 52-week open-label parallel-group, multicentre trial involving adults with mild to moderate asthma. Patients were randomised to budesonide (200 µg, one inhalation via a Turbuhaler two times per day, plus as-needed terbutaline 250 µg, two inhalations via a Turbuhaler as needed; budesonide maintenance group) or budesonide–formoterol (200 µg of budesonide and 6 µg of formoterol, one inhalation via a Turbuhaler as needed; budesonide–formoterol group). The primary outcome was the annualised rate of severe asthma exacerbations.

A key secondary outcome measure in both studies was the ACQ-5 score measured at all trial visits over the course of 52 weeks. The ACQ-5 score is the mean score of five questions that assess asthma symptoms during the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), in which an overall 0.5-unit change represents the MCID.[9 11] The ACQ-5 was measured at every study visit over the course of 52 weeks in both Novel START (weeks 0 (randomisation), 6, 12, 22, 32, 42 and 52) and PRACTICAL (week 0 (randomisation), and weeks 4, 16, 28, 40 and 52).

In Novel START, patients were categorised as having 'well-controlled', 'partly controlled' or 'uncontrolled' asthma according to the 2015 GINA criteria.[12] The GINA level of control over the last 4 weeks was assessed at every study visit over the course of 52 weeks (weeks 0 (randomisation), 6, 12, 22, 32, 42 and 52). GINA categories were not evaluated in PRACTICAL.

Statistical analysis

For the purposes of these analyses, the treatment comparisons are between as-needed budesonide–formoterol and maintenance budesonide plus as-needed salbutamol (Novel START) and between as-needed budesonide–formoterol and maintenance budesonide plus as-needed terbutaline (PRACTICAL).

Counts and proportions expressed as percentages are used to summarise the number of participants in each treatment arm in Novel START (three treatment arms) and PRACTICAL (two treatment arms) and in relation to ACQ boundary points and change from baseline boundary points. The cut points used for ACQ-5 scores were ≤0.75 indicating 'well-controlled', >0.75 to <1.5 'partly controlled' and≥1.5 'inadequately controlled' asthma.[11] The 'End of Study' counts include those participants with a missing value for the last study visit where a single value imputation was used for the last measurement made after the baseline measurement: last observation carried forwards (LOCF). As outlined in footnotes to the tables some participants had no measurements made after the baseline visit and one participant in Novel START was missing a baseline measurement.

Responder categories are based on the MCID for ACQ-5 of 0.5.[9] Results are presented for patients who improved, that is, responders (a decrease from baseline of at least 0.5), patients who worsened (an increase from baseline of at least 0.5) and patients who had no

clinically meaningful difference (a change from baseline of less than 0.5 in either direction). The estimates of association between ACQ improvement from baseline and randomised treatment were by logistic regression. The analysis of this for the 'End of Study' variable does not take into account the imputation procedure. None of these analyses were prespecified and as a result, no p values are reported and the CIs do not take into account Type I error inflation from performing multiple additional statistical tests.

Counts and proportions expressed as percentages were used to summarise the number of participants in each treatment arm in Novel START (three treatment arms) who were in the GINA control level categories 'well-controlled' or 'partly controlled' compared with 'poorly controlled'. The 'End of Study' counts are defined in a similar way to the ACQ description. The estimate of association between particular treatment arms and GINA category is by logistic regression with baseline GINA category treated as a one degree of freedom continuous covariate with a one-unit difference between categories. Similar comments to those made for ACQ are relevant to the single value imputation and the multiplicity issues.

SAS V.9.4 was used.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our post hoc analysis.

RESULTS

In Novel START[1] and PRACTICAL,[10] the mean (95% CI) difference in ACQ-5 scores for as-needed budesonide–formoterol minus budesonide maintenance plus as-needed SABA was 0.14 (0.05 to 0.23) and 0.06 (−0.005 to 0.12), respectively.

Level of asthma symptom control based on ACQ-5 cut-off scores

In Novel START and PRACTICAL, a similar proportion of patients in the as-needed budesonide–formoterol and budesonide maintenance groups had 'well-controlled' asthma (ACQ-5≤0.75) or 'partly controlled' asthma (ACQ-5>0.75 to <1.5) at the end of the study (tables 1 and 2). With the last observation carried forwards approach in Novel START, 126/214 (58.9%) patients in the as-needed budesonide–formoterol group and 132/214 (61.7%) patients in the budesonide maintenance group had 'well-controlled' asthma at the end of the study; 63/214 (29.4%) and 51/214 (23.8%) had 'partly controlled' asthma in the as-needed budesonide–formoterol and budesonide maintenance groups, respectively. In PRACTICAL, 228/434 (52.5%) patients in the as-needed budesonide–formoterol group and 242/431 (56.2%) in the budesonide maintenance had 'well-controlled' asthma; 126/434 (29.0%) and 116/431 (26.9%) had 'partly controlled' asthma in the as-needed budesonide–formoterol and budesonide maintenance groups, respectively.

Table 1 Proportion of participants in each ACQ-5 group category: 'well-controlled' (≤0.75), 'partly controlled' (>0.75 to <1.5) and 'inadequately controlled' (≥1.5) asthma by visit and end of study, Novel START

	Budesonide–formoterol 'as needed', n (%)				Budesonide maintenance two times per day, n (%)			
Visit	N	'Well-controlled' ≤0.75	'Partly controlled' 0.75 to <1.5	'Inadequately controlled' ≥1.5	N	'Well controlled' ≤0.75	'Partly controlled' 0.75 to <1.5	'Inadequately controlled' ≥1.5
Visit 1 (Baseline)	220	71 (32.3)	82 (37.3)	67 (30.5)	225	71 (31.6)	97 (43.1)	57 (25.3)
Visit 2 (Week 6)	208	81 (38.9)	97 (46.6)	30 (14.4)	206	113 (54.9)	70 (34.0)	23 (11.2)
Visit 3 (Week 12)	198	92 (46.5)	71 (35.9)	35 (17.7)	203	121 (59.6)	61 (30.1)	21 (10.3)
Visit 4 (Week 22)	183	94 (51.4)	73 (39.9)	16 (8.7)	182	114 (62.6)	41 (22.5)	27 (14.8)
Visit 5 (Week 32)	174	98 (56.3)	50 (28.7)	26 (14.9)	171	113 (66.1)	37 (21.6)	21 (12.3)
Visit 6 (Week 42)	170	93 (54.7)	51 (30.0)	26 (15.3)	155	101 (65.2)	36 (22.2)	18 (11.6)
Visit 7 (Week 52)*	196	117 (59.7)	55 (28.1)	24 (12.2)	197	123 (62.4)	45 (22.8)	29 (14.7)
End of study (LOCF)†	214	126 (58.9)	63 (29.4)	25 (11.7)	214	132 (61.7)	51 (23.8)	31 (14.5)

*Visit 7 represents ACQ-5 scores collected at withdrawal from the study or at completion of the study (week 52)
†LOCF except if only a baseline reading was available; the number missing any observations after baseline was 6 for budesonide–formoterol 'as needed' and 11 for budesonide maintenance two times per day.
ACQ-5, Asthma Control Questionnaire Version 5; LOCF, last observation carried forward; N, number of patients in each treatment group at each visit; n, number of patients in each ACQ-5 category.

Table 2 Proportion of participants in each ACQ-5 group category: 'well controlled' (≤0.75), 'partly controlled' (>0.75 to <1.5) and 'inadequately controlled' (≥1.5) asthma by visit and end of study, PRACTICAL

	Budesonide–formoterol 'as needed', n (%)				Budesonide maintenance two times per day, n (%)			
Visit	N	'Well-controlled' ≤ 0.75	'Partly controlled' 0.75 to <1.5	'Inadequately controlled' ≥1.5	N	'Well-controlled' ≤0.75	'Partly controlled' 0.75 to <1.5	'Inadequately controlled' ≥1.5
Visit 1 (Baseline)	437	146 (33.4)	170 (38.9)	121 (27.7)	448	154 (34.4)	161 (35.9)	133 (29.7)
Visit 2 (Week 4)	423	169 (40.0)	180 (42.6)	74 (17.5)	427	202 (47.3)	155 (36.3)	70 (16.4)
Visit 3 (Week 16)	409	177 (43.3)	168 (41.1)	64 (15.7)	399	222 (55.6)	113 (28.3)	64 (16.0)
Visit 4 (Week 28)	389	211 (54.2)	116 (29.8)	62 (15.9)	377	211 (56.0)	98 (26.0)	68 (18.0)
Visit 5 (Week 40)	377	198 (52.5)	121 (32.1)	58 (15.4)	367	211 (57.5)	96 (26.2)	60 (16.4)
Visit 6 (Week 52)*	403	220 (54.6)	111 (27.5)	72 (17.9)	406	237 (58.4)	103 (25.4)	66 (16.3)
End of study (LOCF)†	434	228 (52.5)	126 (29.0)	80 (18.4)	431	242 (56.2)	116 (26.9)	73 (16.9)

*Visit 6 represents ACQ-5 scores collected at withdrawal from the study or at completion of the study (week 52)
†LOCF except if only a baseline reading was available; the number missing any observations after baseline was 3 for budesonide–formoterol 'as needed' 17 for budesonide maintenance two times per day.
ACQ-5, Asthma Control Questionnaire Version 5; LOCF, last observation carried forward; n, number of patients in each ACQ-5 category; N, number of patients in each treatment group at each visit.

This means that a similar small proportion of patients had 'inadequately controlled' asthma in each treatment group at the end of both studies: 11.7% vs 14.5% for as-needed budesonide–formoterol versus budesonide maintenance, respectively, in Novel START; and 18.4% and 16.9%, respectively, in PRACTICAL.

Analysis based on change in ACQ-5

In both Novel START and PRACTICAL, most patients either maintained or improved symptom control in terms of change in ACQ-5 from baseline to the end of the study in both treatment groups (figures 1 and 2; online supplemental figure S1 and S2). With a last observation carried forwards approach in Novel START, the proportion of patients who improved from baseline at the end of the study was 82/214 (38.3%) for the as-needed budesonide–formoterol group and 96/214 (44.9%) for the budesonide maintenance group: 108/214 (50.5%) and 89/214 (41.6%) had no change from baseline in the as-needed budesonide–formoterol and budesonide maintenance groups, respectively. In PRACTICAL, 154/434 (35.5%) patients in the as-needed budesonide–formoterol group

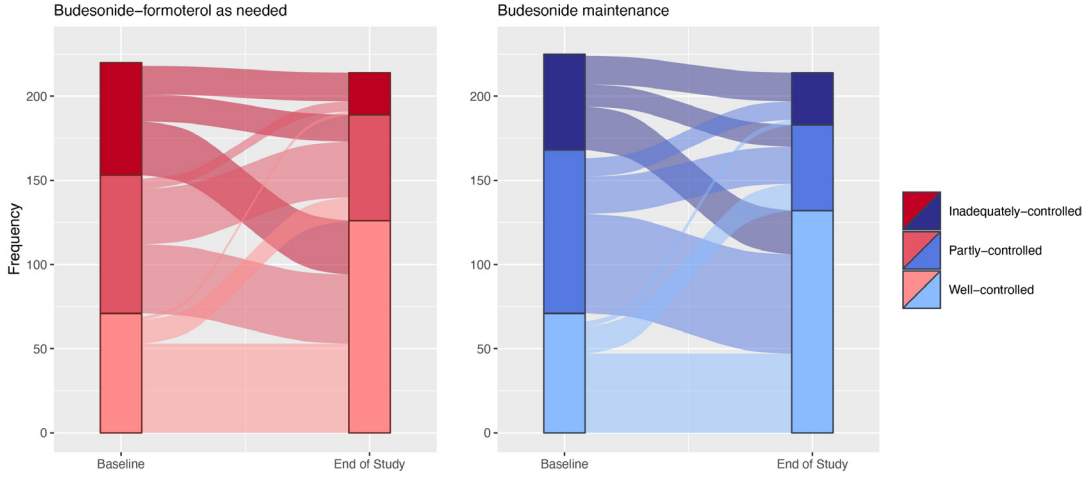

Figure 1 Frequency (n) of participants in each ACQ-5 group category with 'well-controlled' (≤0.75), 'partly controlled' (>0.75 to <1.5) and 'inadequately controlled' (≥1.5) asthma at baseline and end of study (last observation carried forward), and the changes in flow between them, for Novel START. The darkest shades of red and blue denote 'inadequately controlled' asthma, and the lightest shades, 'well-controlled' asthma. The shades between represent 'partly controlled' asthma. The colour of the flow between visits (nodes) represents the ACQ-5 group category at Visit 1. Missing data are excluded. ACQ-5, Asthma Control Questionnaire-5.

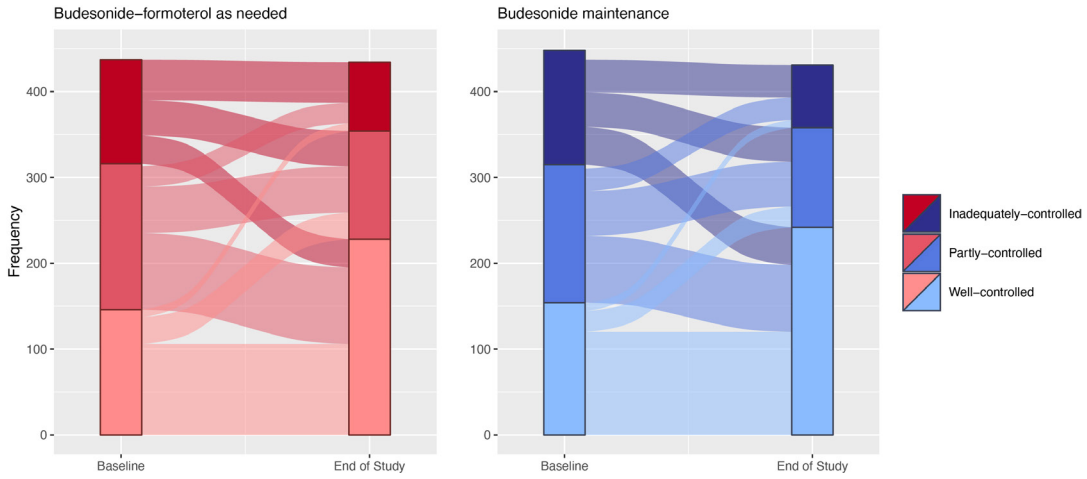

Figure 2 Frequency (n) of participants in each ACQ-5 group category with 'well-controlled' (≤0.75), 'partly controlled' (>0.75 to <1.5) and 'inadequately controlled' (≥1.5) asthma at baseline and end of study (last observation carried forward), and the changes in flow between them, for PRACTICAL. The darkest shades of red and blue denote 'inadequately controlled' asthma and the lightest shades, 'well-controlled' asthma. The shades between represent 'partly controlled' asthma. The colour of the flow between visits (nodes) represents the ACQ-5 group category at visit 1. Missing data are excluded. ACQ-5, Asthma Control Questionnaire-5.

and 169/431 (39.2%) in the budesonide maintenance group improved from baseline; 214/434 (49.3%) and 207/432 (48.0%) had no change from baseline in the as-needed budesonide–formoterol and budesonide maintenance groups, respectively. This means that a similar small proportion of patients had worse asthma symptom control compared with the baseline level of control in both studies: 11.2% vs 13.6% for as-needed budesonide formoterol 'as needed' versus budesonide maintenance in Novel START; and 15.2% vs 12.8%, respectively, in PRACTICAL.

There were no significant differences in the proportion of patients who had clinically important improvements in ACQ-5 by the end of either study: Novel START: OR (95% CI) 0.76 (0.52 to 1.12); PRACTICAL: 0.85 (0.65 to 1.12) (figure 3, tables 3 and 4).

Level of asthma control based on GINA criteria

In Novel START, most patients had 'well-controlled' or 'partly controlled' asthma at the end of the study using the last observation carried forwards approach, and there were no significant differences between the treatment groups (table 5): 183/214 (85.5%) vs 177/214 (82.7%) for as-needed budesonide–formoterol and budesonide maintenance, respectively (OR 1.21, 95% CI 0.71 to 2.05). This means that a similarly small proportion of patients had 'uncontrolled' asthma at the end of the study: 14.5% vs 17.3% for as-needed budesonide–formoterol versus budesonide maintenance, respectively.

DISCUSSION

In both the Novel START and PRACTICAL studies, there were similar proportions of participants in the

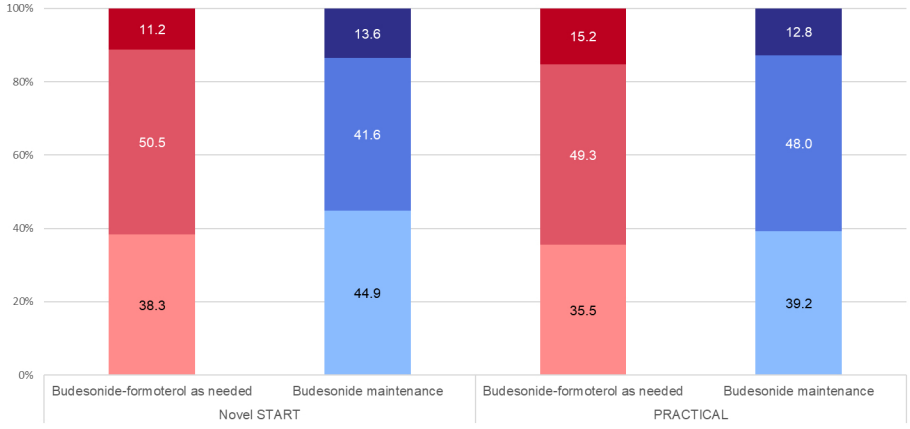

Figure 3 Proportion (%) of participants with clinically relevant changes in ACQ-5 Scores (improved, no difference, worse) from baseline to end of study (last observation carried forward) for Novel START and PRACTICAL. The darkest shades of red and blue denote 'worse' asthma control and the lightest shades, 'improved'. The shades between represent 'no difference'. ACQ-5, Asthma Control Questionnaire-5.

Table 3 Proportion of participants with clinically relevant changes from baseline in ACQ-5 Scores (improved, no difference, worsened) by visit and end of study, Novel START

	Budesonide–formoterol 'as needed' n/N (%)				Budesonide maintenance two times per day n/N (%)			
Visit	N	Improved	No difference	Worsened	N	Improved	No difference	Worsened
Visit 2 (Week 6)	208	58 (27.9)	125 (60.1)	25 (12.0)	206	81 (39.2)	105 (51.0)	20 (9.7)
Visit 3 (Week 12)	198	62 (31.3)	115 (58.1)	21 (10.6)	203	96 (47.3)	92 (45.3)	15 (7.4)
Visit 4 (Week 22)	183	67 (36.6)	101 (55.2)	15 (8.2)	182	92 (50.6)	74 (40.7)	16 (8.8)
Visit 5 (Week 32)	174	62 (35.6)	85 (48.9)	27 (15.5)	171	83 (48.5)	74 (43.3)	14 (8.2)
Visit 6 (Week 42)	170	56 (32.9)	90 (52.9)	24 (14.2)	155	79 (51.0)	62 (40.0)	14 (9.0)
Visit 7 (Week 52)*	196	77 (39.3)	96 (49.0)	23 (11.7)	197	89 (45.2)	80 (40.6)	28 (14.2)
End of study (LOCF)†	214	82 (38.3)	108 (50.5)	24 (11.2)	214	96 (44.9)	89 (41.6)	29 (13.6)

Categories are based on the MCID for ACQ-5 and are defined as follows: improved (a decrease from baseline of at least 0.5); worsened (an increase from baseline of at least 0.5) and no difference (an increase or decrease from baseline of less than 0.5).
*Visit 7 represents ACQ-5 scores collected at withdrawal from the study or at completion of the study (week 52)
†LOCF except if only a baseline reading was available; the number missing any observations after baseline was 6 for budesonide–formoterol 'as needed' and 11 for budesonide maintenance two times per day.
ACQ-5, Asthma Control Questionnaire Version 5; LOCF, last observation carried forward; MCID, minimal clinically important difference; n, number of patients in each ACQ-5 category; short-acting β2-agonist (salbutamol); N, number of patients in each treatment group at each visit.

as-needed budesonide–formoterol and the maintenance budesonide plus SABA groups that had 'well-controlled' or 'partly controlled' asthma at the end of the study, when assessed by ACQ-5 score or GINA-defined levels of control. Furthermore, the proportions of patients who either improved or were unchanged from baseline at the end of the study were similar in the two treatment groups. These findings complement previous analyses which showed that the mean differences in ACQ-5 with as-needed budesonide–formoterol compared with maintenance budesonide in the Novel START and PRACTICAL studies were 0.14 (95% CI 0.05 to 0.23)[1] and 0.06 (95% CI −0.005 to 0.12),[10] respectively. In both studies, the upper limits of the 95% CIs were much less than the MCID of 0.50.[9] Thus, these post hoc analyses support the interpretation that the small mean differences in asthma symptom control between as-needed budesonide–formoterol and maintenance budesonide plus as-needed SABA reported in randomised controlled trials are unlikely to be clinically important in real-world clinical practice.[1 2 10 13]

Table 4 Proportion of participants with clinically relevant changes in ACQ-5 score from baseline (improved, no difference, worsened) by visit and end of study, PRACTICAL

	Budesonide–formoterol 'as needed', n (%)				Budesonide maintenance two times per day N (%)			
Visit	N	Improved	No difference	Worsened	N	Improved	No difference	Worsened
Visit 2 (Week 4)	423	111 (26.2)	253 (59.8)	59 (14.0)	427	128 (30.0)	254 (59.5)	45 (10.5)
Visit 3 (Week 16)	409	126 (30.8)	226 (55.3)	57 (13.9)	399	144 (36.1)	209 (52.4)	46 (11.5)
Visit 4 (Week 28)	389	132 (33.9)	202 (51.9)	55 (14.1)	377	130 (34.5)	199 (52.8)	48 (12.7)
Visit 5 (Week 40)	377	126 (33.4)	196 (52.0)	55 (14.6)	367	132 (36.0)	193 (52.6)	42 (11.4)
Visit 6 (Week 52)*	403	143 (35.5)	200 (49.6)	60 (14.9)	406	158 (38.9)	196 (48.3)	52 (12.8)
End of study (LCOF)†	434	154 (35.5)	214 (49.3)	66 (15.2)	431	169 (39.2)	207 (48.0)	55 (12.8)

Categories are based on the MCID for ACQ-5 and are defined as follows: improved (≤−0.5); no change (>0.5 to <0.5), worsened (≥0.5).
*Visit 6 represents ACQ-5 scores collected at withdrawal from the study or at completion of the study (week 52).
†LOCF except if only a baseline reading was available; the number missing any observations after baseline was 3 for budesonide–formoterol 'as needed' 17 for budesonide maintenance two times per day.
ACQ-5, Asthma Control Questionnaire Version 5; LOCF, last observation carried forward; MCID, minimal clinically important difference; N, number of patients in each treatment group at each visit; n, number of patients in each ACQ-5 category.

Table 5 Proportion of participants in each GINA category ('well' and 'partly' controlled vs 'uncontrolled') by visit and end of study, Novel START

	Budesonide–formoterol 'as needed'			Budesonide maintenance two times per day		
	N	Well/partly controlled	Uncontrolled	N	Well/partly controlled	Uncontrolled
Visit		n/N (%)	n/N (%)		n/N (%)	n/N (%)
Visit 1 (Baseline)	220	167 (75.9)	53 (24.1)	225	162 (72.0)	63 (28.0)
Visit 2 (Week 6)	208	165 (79.3)	43 (20.7)	206	180 (87.4)	26 (12.6)
Visit 3 (Week 12)	198	162 (81.8)	36 (18.2)	203	177 (87.2)	26 (12.8)
Visit 4 (Week 22)	183	153 (83.6)	30 (16.4)	182	163 (89.6)	19 (10.4)
Visit 5 (Week 32)	174	143 (82.2)	31 (17.8)	171	151 (88.3)	20 (11.7)
Visit 6 (Week 42)	170	140 (82.4)	30 (17.7)	155	130 (83.9)	25 (16.1)
Visit 7 (Week 52)*	196	166 (84.3)	31 (15.7)	197	161 (81.7)	36 (18.3)
End of study (LOCF)†	214	183 (85.5)	31 (14.5)	214	177 (82.7)	37 (17.3)

The definitions for GINA level of asthma control were based on the GINA report published in 2014.
*Visit 7 represents ACQ-5 scores collected at withdrawal from the study or at completion of the study (week 52)
†LOCF except if only a baseline reading was available; the number missing any observations after baseline was 6 for budesonide–formoterol 'as needed' and 11 for budesonide maintenance two times per day.
ACQ-5, Asthma Control Questionnaire Version 5; GINA, Global Initiative for Asthma; LOCF, last observation carried forward; N, number of patients in each treatment group at each visit; n, number of patients in each GINA category.

Of clinical relevance, the similar levels of asthma control in the two groups occurred despite the as-needed budesonide–formoterol regimen relying on symptoms to trigger its use (whereas maintenance therapy is taken regularly two times per day with the aim of preventing symptoms) and ICS exposure with as-needed budesonide–formoterol being 52% and 42% lower than with maintenance budesonide in the Novel START and PRACTICAL studies, respectively.[1 10] This suggests that in mild asthma the timing of the ICS dose may be a more important determinant of asthma control than the total dose.

The generalisability of the study findings to real-world clinical practice, in which adherence to regular scheduled maintenance treatment is considerably lower than in clinical trials, is another important consideration.[14–16] It is likely that the relative efficacy of budesonide maintenance treatment is lower in the real-world compared with a clinical trial setting for this reason, thereby resulting in lesser degree of asthma control. In contrast, budesonide–formoterol reliever relies on a patient's natural behaviour to treat their symptoms when they arise and thus this treatment approach is less susceptible to adherence issues and is more likely to reflect real-world efficacy.

We acknowledge that none of these analyses were prespecified in the original study protocols, and should be regarded as exploratory. For this reason, no CIs account for type I error inflation by performing multiple additional statistical tests. The principal results use a last observation carried forwards approach to single value imputation, and we accept that this approach might add to the imprecision of our findings. A further limitation is that the use of patient-reported outcome measures, such as the ACQ-5, in open-label studies may introduce bias as patients are aware of their randomised treatment, which in turn may influence their responses. However, similar ACQ-5 results were reported in the double-blind SYGMA 1 and 2 studies,[2 13] which supports the validity of the Novel START and PRACTICAL results.

In conclusion, our analyses did not identify clinically important differences in the proportions of patients with 'well-controlled' or 'partly controlled' asthma or proportions who either improved or maintained their level of symptom control with as-needed budesonide–formoterol versus maintenance budesonide plus SABA treatment in the Novel START and PRACTICAL studies. The findings support the interpretation that the small differences in mean asthma symptom control between as-needed budesonide–formoterol and maintenance budesonide plus as-needed SABA seen in randomised controlled trials are unlikely to translate to clinically important differences when treatment is used in routine clinical practice.

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Contributors RB conceived the work. MW and AE conducted the statistical analysis. LH, AE and PB designed the figures. LH and RB wrote the first draft of the manuscript. All authors were involved in the interpretation of the data, and critically revising and approving the final version of the manuscript for publication. All authors agreed to be accountable for all aspects of the work. RB accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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