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 beta2-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 376/434 (82.7%) 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.

INTRODUCTION

In mild asthma, budesonide–formoterol reliever therapy alone reduces the risk of severe exacerbations compared with short-acting beta2-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.5

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,5 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-alone 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 differed, 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 and PRACTICAL 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.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.14 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.

**RESULTS**

In Novel START and PRACTICAL, 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 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.

**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

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

†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.

Hatter L, et al. BMJ Open Resp Res 2022;9:e001271. doi:10.1136/bmjresp-2022-001271
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
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
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) and 0.06 (95% CI −0.005 to 0.12), respectively. In both studies, the upper limits of the 95% CIs were much less than the MCID of 0.50. 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.

| 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 |
|---------|----------------------------------------------------------------------------------|
| Visit   | Budesonide–formoterol 'as needed' n/N (%)                                      | Budesonide maintenance two times per day n/N (%) |
|         | 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.

| 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 |
|---------|----------------------------------------------------------------------------------|
| Visit   | Budesonide–formoterol 'as needed', n (%)                                      | Budesonide maintenance two times per day N (%) |
|         | 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 (LOCF)† | 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.
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.

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

| Visit        | Budesonide–formoterol ‘as needed’ |          |          | Budesonide maintenance two times per day |          |          |
|--------------|-----------------------------------|----------|----------|------------------------------------------|----------|----------|
|              | N                                 | Well/partly controlled | Uncontrolled | N                                 | Well/partly controlled | Uncontrolled |
| 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.

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