Budesonide–formoterol reliever therapy in intermittent *versus* mild persistent asthma

To the Editor:

Traditional asthma maintenance therapy in adults and adolescents comprises inhaled corticosteroids (ICS), with a long-acting β_2-agonist (LABA) added if ICS monotherapy provides insufficient control [1, 2]. For patients with symptoms occurring on two or fewer occasions per week (so-called "intermittent" asthma [2]), who may represent around one-third of the asthma population [3], many guidelines still recommend short-acting β_2-agonist (SABA) rescue medication alone [2, 4]. However, SABA-only treatment is still associated with severe exacerbations [5], the incidence of which is almost halved with low-dose maintenance ICS in intermittent asthma [6], but adherence is poor [7, 8]. Since 2019, the Global Initiative for Asthma (GINA) strategy document has advised against SABA monotherapy, even in those with symptoms occurring on fewer than two occasions per month [9, 10]. Instead, ICS therapy is now recommended whenever rescue medication is taken, either as combined ICS–formoterol, or a separate ICS inhaler [9]. However, evidence supporting this in patients with symptoms occurring on two or fewer occasions per week is limited.

NovelSTART was a 52-week, randomised, open-label, parallel-group study in adults with mild asthma [11]. Eligible patients were using SABA as sole asthma therapy, and had either at least one severe exacerbation in the previous 12 months, or used SABA on at least two occasions in the previous 4 weeks. Patients were randomised to: salbutamol 100 µg two inhalations as-needed; maintenance budesonide 200 µg twice daily plus as-needed salbutamol; or combination budesonide–formoterol 200/6 µg, one inhalation as needed. Overall, as-needed budesonide–formoterol reduced severe exacerbation risk compared with both as-needed salbutamol and maintenance budesonide plus as-needed salbutamol [11], with the effect modulated by the T2 inflammatory profile [12].

Since patients could have used SABA just twice in the previous four weeks (or not at all if they had a severe exacerbation in the previous 12 months) NovelSTART provides the first opportunity to assess the efficacy of as-needed budesonide–formoterol in intermittent asthma. We therefore conducted *post hoc* analyses, with "intermittent asthma" defined as use of SABA alone on two or fewer occasions per week in the 4 weeks before entry, and with no severe exacerbation in the previous year. The comparator subgroup had "mild persistent asthma", using SABA alone on more than two occasions per week (but less than twice daily) in the previous 4 weeks, and/or one or more severe exacerbation in the previous year.

In these current analyses, the main comparisons were between as-needed budesonide–formoterol and as-needed salbutamol. The associations between asthma exacerbations, randomised treatment and intermittent *versus* persistent subgroup were analysed by Poisson regression with an offset for time in study, severe exacerbations by logistic regression, and Asthma Control Questionnaire (ACQ)-5 by analysis of covariance with baseline value as continuous covariate (SAS v9.4). Interaction terms between treatment and subgroup evaluated differences between subgroup responses. There was no adjustment for multiple analyses.

A total of 668 participants were included, 335 (50.1%) with intermittent asthma. At baseline, this subgroup had lower SABA use than the mild persistent subgroup (1.3 *versus* 5.6 times per week), lower ACQ-5 score (0.93 *versus* 1.26), and similar prebronchodilator forced expiratory volume in 1 s (90.2 *versus* 89.4%). In the mild persistent subgroup, 15% had a severe exacerbation in the previous 12 months. Median

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These *post hoc* analyses of NovelSTART provide the first evidence that the exacerbation risk reduction with budesonide–formoterol reliever therapy *versus* salbutamol reliever therapy is similar in adults with intermittent and mild persistent asthma https://bit.ly/3iiRKqR

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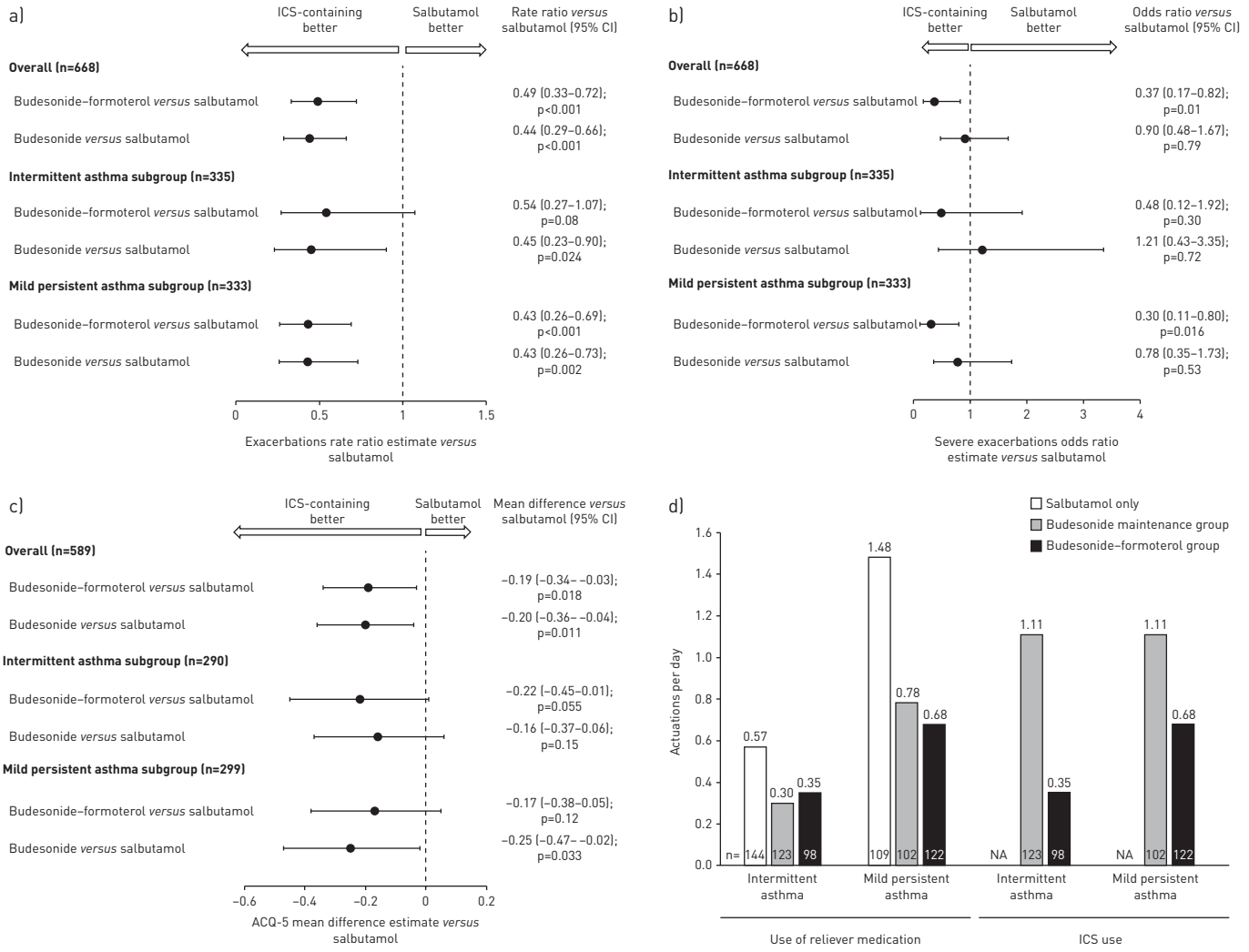

FIGURE 1 a) All exacerbations: rate ratios for budesonide–formoterol or budesonide maintenance *versus* salbutamol only. b) Severe exacerbations: odds ratios for budesonide–formoterol or budesonide maintenance *versus* salbutamol only. c) Asthma Control Questionnaire (ACQ)-5 score at week 52: mean differences for budesonide–formoterol or budesonide maintenance *versus* salbutamol only. d) Mean reliever and inhaled corticosteroid (ICS) use over the course of the trial from electronic monitoring.

(interquartile range) blood eosinophil counts were similar in the two subgroups (0.22 (0.13–0.32) *versus* 0.23 (0.15–0.40) $\times 10^9 \cdot L^{-1}$), as were fractional exhaled nitric oxide levels (35 (19–67) *versus* 40 (21–79) ppb).

Overall, exacerbation rates per year were lower in the intermittent than the mild persistent asthma subgroup (salbutamol: 0.265 *versus* 0.554; maintenance budesonide: 0.120 *versus* 0.241; as-needed budesonide–formoterol: 0.143 *versus* 0.236 respectively). Rate ratios *versus* salbutamol were similar with no evidence that the relative effects of ICS-containing treatments differed between the two subgroups (figure 1a; p-interaction 0.85).

Few patients had severe exacerbations in some subgroups. In the intermittent subgroup 6.1, 7.3 and 3.1% patients receiving salbutamol, maintenance budesonide and budesonide–formoterol experienced a severe exacerbation, respectively, compared with 14.7, 11.8 and 4.9% in the mild persistent subgroup. Patients receiving budesonide–formoterol had a lower risk of severe exacerbations than salbutamol, with no difference between maintenance budesonide and salbutamol (figure 1b). There was no evidence of a difference in relative treatment effects by subgroup (p-interaction 0.76).

ACQ-5 at week 52 was consistent with greater effectiveness of the ICS-containing therapies *versus* salbutamol in the overall analysis, with the relative effects similar in the two subgroups (figure 1c; p-interaction 0.66). For as-needed salbutamol, both alone and with maintenance budesonide, mean use in the intermittent subgroup was 38.5% of that with mild persistent asthma (figure 1d). Use of budesonide–formoterol in the intermittent subgroup was 51.4% of that with mild persistent asthma. Use of maintenance budesonide was similar in the two subgroups.

These findings help to address the evidence gap for the use of ICS–formoterol as sole reliever therapy in adults with intermittent asthma who would not qualify for any ICS treatment by some guidelines. In addition, although recommended by international guidelines [9], the evidence for ICS used according to this regimen in intermittent asthma is scarce. Given poor adherence in asthma to inhaled therapy, especially to maintenance ICS [7, 8], ICS–formoterol as-needed is a more practical option for patients with symptoms occurring on two or fewer occasions per week than expecting them to use daily ICS; combining bronchodilation with anti-inflammatory therapy is a regimen that is consistent with patients' desire for symptom relief [13]. Indeed, most patients who experienced the as-needed ICS–formoterol strategy in another clinical trial preferred it to maintenance ICS plus as-needed SABA [14]. Our analyses suggest that as-needed ICS–formoterol is likely to be at least as effective as maintenance ICS in patients with intermittent asthma.

The present findings confirmed that the intermittent asthma definition identified a group that differed from mild persistent asthma in terms of baseline symptoms and severe exacerbation history. As symptom burden in this population is relatively low, the rationale for ICS or as-needed budesonide–formoterol use to reduce the population-level risk of exacerbations becomes compelling, which is also consistent with the primary outcome of the original study. Furthermore, the lower exacerbation risk and low use of salbutamol reliever in the intermittent asthma subgroup during the study demonstrated the stability of this trait. In addition, the greater reduction in severe exacerbation risk with budesonide–formoterol than that observed with maintenance budesonide, despite about half the mean dose of budesonide overall, adds further support to the timing of ICS use being more important than total ICS dose taken in reducing severe exacerbation risk, as reported from an analysis of the related PRACTICAL study [15].

A key strength of the current analyses is that the subgroups were similar in size, as were the treatment groups within each subgroup. Limitations include that these were *post hoc*, unpowered analyses from a single, open-label study, which therefore need to be confirmed in a prospectively designed study. In addition, the low rate of exacerbations during the study limit the conclusions that can be drawn.

In conclusion, these *post hoc* subgroup analyses challenge the current recommendations in many guidelines, that patients with symptoms or SABA use twice a week or less should be treated only with as-needed SABA. The results show that the greater efficacy of as-needed budesonide-formoterol over as-needed salbutamol, particularly for reduction in risk of exacerbations, is similar in intermittent and mild persistent asthma without the requirement for daily treatment. Importantly, these findings provide support to the recommendations in GINA 2019 onwards for the use of as-needed low dose ICS–formoterol by patients with asthma who have infrequent symptoms, who comprise a sizeable proportion of the overall asthma population.

Alberto Papi[1], Irene Braithwaite[2], Stefan Ebmeier[2], Robert J. Hancox[3,4], Tim Harrison[5], Mark Holliday[2], Claire Houghton[2], Luca Morandi[1], Karen Oldfield[2], Ian D. Pavord[6], Helen K. Reddel[7], Mathew Williams[2], Mark Weatherall[8] and Richard Beasley[2,9] on behalf of the NovelSTART Study Team

[1]Respiratory Medicine Unit, Dept of Morphology, Surgery and Experimental Medicine, Università di Ferrara, Ferrara, Italy. [2]Medical Research Institute of New Zealand, Wellington, New Zealand. [3]Dept of Respiratory Medicine, Waikato Hospital, Hamilton, New Zealand. [4]Dept of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand. [5]Nottingham NIHR Biomedical Research Centre, University of Nottingham, Nottingham, UK. [6]Oxford Respiratory NIHR BRC, Nuffield Dept of Medicine, University of Oxford, Oxford, UK. [7]Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia. [8]University of Otago Wellington, Wellington, New Zealand. [9]Capital and Coast District Health Board, Wellington, New Zealand.

Correspondence: Alberto Papi, Respiratory Medicine Unit, Dept of MSEM, Morphology, Surgery and Experimental Medicine, University of Ferrara, Via Aldo Moro 8, 44124 Ferrara, Italy. E-mail ppa@unife.it

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