

Reply to "As-needed budesonide-formoterol for adolescents with mild asthma: importance of lung function"



To the Editor:

We thank Shanthikumar and Robinson for their comments about our paper on as-needed budesonide-formoterol compared with as-needed short-acting beta₂-agonist (SABA) alone, or with maintenance budesonide plus as-needed SABA, in adolescents with mild asthma,¹ in which they questioned the potential long-term consequences of as-needed budesonide-formoterol on lung growth, adult lung function decline, and all-cause mortality in adulthood.²

The authors' concern relates to the reported 2.3% difference over 12 months in change in pre-bronchodilator forced expiratory volume in 1 second (FEV₁) % predicted with as-needed budesonide-formoterol compared with maintenance inhaled corticosteroids (ICS), which was statistically significant in Symbicort Given as Needed in Mild Asthma (SYGMA) 1 (highly controlled, frequent visits, twice-daily adherence reminders, diary, and lung function) and in the pooled data from SYGMA 1 and 2, but not observed in SYGMA 2 (more pragmatic, no diary/reminders,

only 2 midstudy visits).¹ We agree that these findings require further evaluation, preferably in longer-term studies.

However, it is reassuring that further analyses show no significant differences in post-bronchodilator forced vital capacity (FVC; mL) between treatments in SYGMA 1 or SYGMA 2 adolescents or, indeed, in adults—the FVC trajectories over 12 months were almost identical (Figure 1). These data fail to support the correspondents' hypothesis that lung growth was compromised.

Pre-bronchodilator FEV₁ has sometimes been used as a marker of lung growth^{3,4} and, as the correspondents observe, has been linked with some long-term sequelae.⁵ However, in epidemiological studies of obstructive lung disease, post-bronchodilator FVC is preferred,⁶ and has a different trajectory to FEV₁ during lung growth that is affected by the presence of asthma.⁴ In most papers cited in this correspondence,² the associations with adverse outcomes during adulthood were with FVC rather than FEV₁, although sometimes with both.⁵ In asthma populations, pre-bronchodilator FEV₁ is more variable and susceptible to changes in day-to-day asthma control that may explain differences in comparisons of pre-bronchodilator FEV₁ and post-bronchodilator FVC in ours and other studies.^{1,5}

The common assumption that regular ICS are needed to prevent impaired lung growth and/or accelerated decline in lung function in asthma is not supported by the findings of long-term studies. In

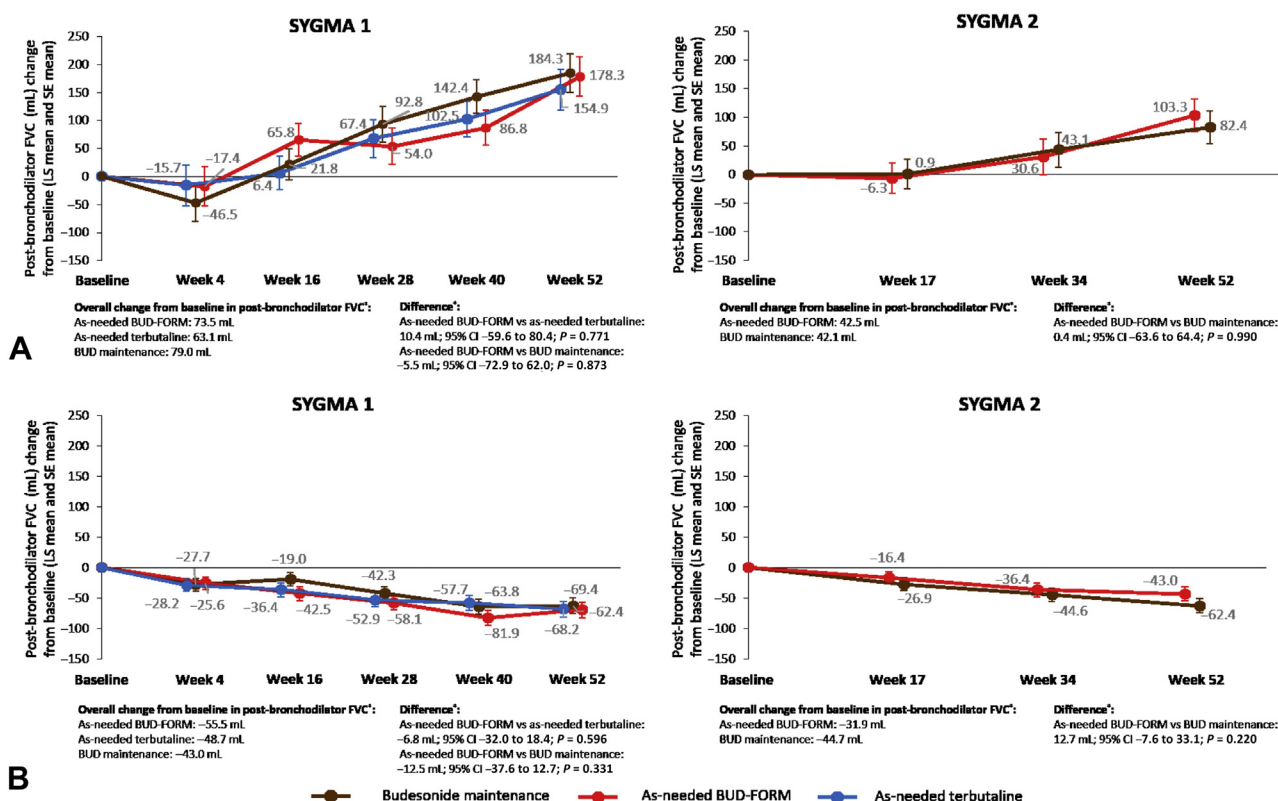


FIGURE 1. Change in post-bronchodilator FVC (mL) by treatment over 52 weeks in (A) adolescents and (B) adults. *Statistical analysis model: Mixed-effects model for repeated measures with randomized treatment, prestudy treatment, region, sex, visit, and randomized-treatment visit as fixed effects. The patient is included as a random effect and baseline FVC (mL), age, and height as continuous covariates. The variance-covariance matrix is assumed to be unstructured. Estimates are LS Means. "Overall" is the estimate across all treatment visits. BUD, Budesonide; BUD-FORM, budesonide-formoterol; LS, least squares; SE, standard error.

long-term follow-up of the Childhood Asthma Management Program (CAMP) study, there was no difference in lung function trajectories according to whether or not patients received ICS.³ Instead, predictors of reduced lung growth included prednisone courses and other measures of severe persistent symptomatic asthma.³ A recent systematic review found that, whereas ICS improved pre-bronchodilator FEV₁, there were only limited observational data for post-bronchodilator outcomes,⁷ and the authors concluded that there was “insufficient evidence to determine whether [ICS] treatment reduces the incidence of fixed airflow obstruction in later life.”⁷ This is especially true for mild asthma. Without such data, linking long-term consequences such as all-cause mortality with small differences in pre-bronchodilator FEV₁ over 12 months seems highly speculative.

Instead, the much more immediate concern that should be empathically discussed with adolescents and families is that most adolescents, if prescribed daily ICS, are poorly adherent, increasing their risk of serious exacerbations and corticosteroid load. The reduction in these risks, without the need for daily treatment or concern about growth, led to our conclusion that as-needed budesonide-formoterol is a safe and effective alternative option for adolescents with mild asthma.

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