Original Article

Efficacy and Safety of As-Needed Budesonide-Formoterol in Adolescents with Mild Asthma

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What is already known about this topic? Low-dose inhaled corticosteroid treatment can reduce the risk of severe exacerbations and improve symptom control in patients with mild asthma, but poor adherence to maintenance therapy and reliance on short-acting β_2-agonists remain significant challenges in adolescent patients.

What does this article add to our knowledge? In adolescents with mild asthma, as-needed budesonide-formoterol reduced the risk of severe exacerbations versus short-acting β_2-agonist alone, with similar efficacy to maintenance inhaled corticosteroid. There was no evidence of growth suppression in adolescents treated with as-needed budesonide-formoterol.

How does this study impact current management guidelines? The finding that as-needed budesonide-formoterol is a safe and viable treatment option in adolescent patients, without the need for daily maintenance treatment, supports the Global INitiative for Asthma positioning of as-needed inhaled corticosteroid-formoterol as preferred reliever in adolescents with mild asthma.

BACKGROUND: Medication adherence is challenging for adolescents. In mild asthma, as-needed budesonide-formoterol (BUD-FORM) reduces severe exacerbations compared with as-needed short-acting beta$_2$-agonists, similar to the reduction with maintenance budesonide.

OBJECTIVE: This *post hoc* pooled analysis of Symbicort Given as-needed in Mild Asthma (SYGMA) 1 and 2 assessed the efficacy and safety of as-needed BUD-FORM in adolescents.

METHODS: SYGMA 1 and 2 were 52-week, double-blind studies (NCT022149199; NCT02224157) in patients 12 years

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Abbreviations used
ACQ-5- 5-item Asthma Control Questionnaire
AE- Adverse event
BUD-FORM- Budesonide-formoterol
FEV1- forced expiratory volume in 1 second % predicted
GINA- Global INitiative for Asthma
ICS- Inhaled corticosteroid
OCS- oral corticosteroids
SABA- Short-acting β_2-agonist
SYGMA- Symbicort Given as-needed in Mild Asthma

or older with mild asthma. Patients were randomized to twice-daily placebo + as-needed BUD-FORM 200/6 μg, twice-daily BUD 200 μg + as-needed terbutaline (BUD maintenance), or twice-daily placebo + as-needed terbutaline 0.5 mg (SYGMA 1 only). Annualized severe exacerbation rates, maintenance treatment adherence, and safety (including change in height) were compared between treatment groups in adolescents (aged ≥12 to <18 years).
RESULTS: Severe exacerbation rate was similar with as-needed BUD-FORM and BUD maintenance (pooled analysis: 0.08 vs 0.07/y; $P = .634$), and was significantly lower with as-needed BUD-FORM versus as-needed terbutaline (SYGMA 1: 0.04 vs 0.17/y; $P = .005$). Median adherence was 73% in SYGMA 1 and 51% in SYGMA 2. Change in height from baseline in adolescents aged ≥12 years to <14 years was significantly greater with as-needed BUD-FORM (4.8 cm) versus BUD maintenance (3.9 cm) (pooled: $P < .046$), and was similar between as-needed BUD-FORM (4.5 cm) and as-needed terbutaline (4.1 cm) (SYGMA 1: $P = .500$). No new or unexpected safety concerns were identified.
CONCLUSIONS: In adolescents with mild asthma, as-needed BUD-FORM was superior to as-needed terbutaline for severe exacerbation reduction, with similar efficacy to BUD maintenance. As-needed BUD-FORM provides an alternative treatment option for adolescents with mild asthma, without needing daily treatment. **(J Allergy Clin Immunol Pract 2021;9:3069-77)**

Key words: *Adherence; Adolescent; As-needed; Budesonide-formoterol; Exacerbations; Mild asthma*

INTRODUCTION

Adolescence is a period of rapid physical, emotional, cognitive, and social changes, bringing particular issues for adolescents with chronic health conditions such as asthma.[1,2] Treatment of asthma with low-dose inhaled corticosteroids (ICS) can reduce the risk of severe exacerbations and offer good symptom control, including in mild asthma,[3] but poor adherence[4-8] and overreliance on as-needed short-acting β_2-agonists (SABA)[9] are significant barriers. A rapid reduction in adherence to ICS-containing medications has been reported during adolescence, falling from 50% adherence at age 12 years to less than 20% at age 17 years.[8,10] Factors contributing to poor adherence among children and adolescents include concern about potential adverse effects of ICS, including effects on growth.[11,12] Poor adherence can result in a loss of asthma symptom control and increase in exacerbations, significantly decreasing quality of life and resulting in hospitalizations and school absenteeism,[13,14] which further isolate adolescents from their peers.[15,16] Furthermore, evidence suggests that poor disease management established in adolescence may be carried into young adulthood.[9]

Asthma is estimated to be mild in 50% to 75% of patients, across all age groups.[17] Mild asthma may not always be associated with troublesome symptoms, but patients remain at risk of severe exacerbations, with mild asthma accounting for 30% to 40% of exacerbations resulting in emergency department visits.[17] The SYGMA (Symbicort Given as-needed in Mild Asthma) trials[18,19] examined the efficacy of as-needed budesonide-formoterol (BUD-FORM) in patients 12 years or older with mild asthma. Across the whole age range, SYGMA 1 demonstrated that treatment with as-needed BUD-FORM resulted in a significantly lower 1-year severe exacerbation rate versus as-needed terbutaline, with similar efficacy to BUD maintenance plus as-needed terbutaline. In SYGMA 2, similar severe exacerbation rates over 12 months were observed between as-needed BUD-FORM and BUD maintenance.[19] In both studies, there was no clinically important difference in symptom control or lung function compared with twice-daily low-dose ICS, and the reduction in risk of severe exacerbations was achieved with less than a quarter of the average ICS dose.[18,19]

The evidence from the SYGMA studies provided the basis for a major change in 2019 in asthma management, with the Global INitiative for Asthma (GINA) report recommending against treatment of asthma in adults and adolescents with SABA alone.[20] Instead, for patients with symptoms twice a month or more (Step 2), GINA now recommends as-needed combination low-dose ICS-formoterol as an alternative to regular low-dose ICS plus as-needed SABA, and as the only "preferred" treatment for patients with symptoms less than twice a month (Step 1).[20,21] The safety of BUD-FORM up to a total of 12 inhalations in a day (total FORM 72 μg metered dose or 54 μg delivered dose) has been established in randomized controlled trials of maintenance and reliever therapy in more than 22,000 patients,[22] including adolescents,[23] and now in studies of mild asthma involving almost 10,000 patients.[18,19,24,25]

Regulatory authorities encourage research on the efficacy and safety of pharmaceutical interventions in adolescent populations, highlighting the unique issues for adolescents of rapid physical growth, hormonal changes, ongoing neurocognitive development, and the transition to assuming responsibility for their own health and medication-taking, emphasizing the particular problems of poor adherence in this age group.[26] Adverse events (AEs), too, may not be the same as in adults. This *post hoc* pooled analysis of the adolescent subgroup in the SYGMA 1 and 2 trials was therefore conducted to evaluate the efficacy of as-needed BUD-FORM in reducing severe exacerbations and improving symptom control and lung function, to assess adherence to randomized maintenance treatment, and to investigate the safety of the 3 treatment regimens in adolescents with mild asthma.

METHODS

The SYGMA 1 (NCT02149199) and SYGMA 2 (NCT02224157) trials were 52-week, double-blind, randomized,

multinational, parallel-group studies.[18,19] The design of the 2 studies has been described in detail.[27]

Trial designs and patients

Briefly, patients 12 years or older with clinically diagnosed mild asthma according to GINA (2012) criteria[21] for at least 6 months before the study entry were eligible. Patients were stratified by pre-study treatment, with asthma either uncontrolled on bronchodilators or controlled on ICS or leukotriene receptor antagonists at study entry as judged by the investigators.

Eligible patients entered a 2- to 4-week run-in period before randomization in which they only received as-needed terbutaline 0.5 mg (Bricanyl) via Turbuhaler. Patients requiring as-needed terbutaline on 3 or more separate days during the last week of the run-in period, and therefore considered to need Step 2 treatment by GINA 2012 criteria, proceeded to randomization.[18,19]

In SYGMA 1, patients were randomized to receive twice-daily placebo plus as-needed terbutaline 0.5 mg (Bricanyl Turbuhaler, AstraZeneca; corresponding to a delivered dose of 0.4 mg), twice-daily placebo plus as-needed BUD-FORM 200/6 μg (Symbicort Turbuhaler, AstraZeneca; corresponding to a delivered dose of 160/4.5 μg) (herein referred to as as-needed BUD-FORM), or twice-daily BUD 200 μg (Pulmicort Turbuhaler, AstraZeneca) as maintenance, plus as-needed terbutaline 0.5 mg (Bricanyl Turbuhaler, AstraZeneca) (herein referred to as BUD maintenance). In SYGMA 2, patients were randomized to receive as-needed BUD-FORM or BUD maintenance.

Patients were instructed to take 1 inhalation from their maintenance inhaler every morning and evening, and to take 1 inhalation from their as-needed inhaler to relieve asthma symptoms. During the treatment period, patients were instructed that if they needed more than 12 inhalations from their as-needed inhaler in a single day, they should contact the investigator for reassessment of their condition. Inhaler use was electronically recorded in both SYGMA 1 and SYGMA 2. In SYGMA 1, patients received twice-daily eDiary adherence reminders for the duration of the study, and had 5 mid-study visits. In SYGMA 2, there was no eDiary and no adherence reminders, and only 2 mid-study visits.

Study end points and analysis

This *post hoc* pooled analysis of adolescent subgroup data (patients aged ≥12 to <18 years) from the SYGMA trials investigated the efficacy of as-needed BUD-FORM versus as-needed terbutaline and BUD maintenance on annual severe exacerbation rates, time to first severe exacerbation, lung function (forced expiratory volume in 1 second [FEV_1] % predicted), 5-item Asthma Control Questionnaire (ACQ-5) scores, adherence to randomized maintenance treatment (placebo in the as-needed BUD-FORM and as-needed terbutaline arms, BUD in the BUD maintenance arm), ICS daily dose, and safety outcomes including mean change in height from baseline (to assess potential impact of ICS use on growth), AEs, and severe AEs. Patient height was measured according to the local practices at investigators' sites.

Data from SYGMA 1 were used for the comparison of as-needed BUD-FORM versus as-needed terbutaline, and data from SYGMA 1, SYGMA 2, and pooled data from both studies were used to estimate the treatment effect of as-needed BUD-FORM versus BUD maintenance. In SYGMA 1 and 2, number of severe exacerbations was analyzed by a negative binomial model including randomized treatment, pre-study asthma treatment, and number of severe exacerbations in last 12 months (0, ≥1), with follow-up time as an offset variable. The same negative binomial model was used to analyze severe exacerbations in the pooled analysis, with study and region also included as factors. Confidence intervals (CIs) and hazard ratios for the analysis of time to first severe exacerbation in SYGMA 1 and SYGMA 2 were derived using a Cox regression model with randomized treatment, pre-study asthma treatment, and severe exacerbations in the last 12 months (0, ≥1) as covariates. Study and region were also included as covariates in the analysis of time to first severe exacerbation in the pooled population. In SYGMA 1 and SYGMA 2, changes from baseline in FEV_1 % predicted and ACQ-5 scores were analyzed on the basis of a mixed model for repeated measures, with randomized treatment, pre-study asthma treatment, region, visit, and randomized treatment-by-visit interaction as fixed effects, baseline values as a covariate, and subject as a random effect. In the pooled analysis, changes from baseline to treatment average in FEV_1 % predicted and ACQ-5 scores were analyzed by an analysis of covariance model, with randomized treatment, pre-study asthma treatment, region, and study as factors, and the corresponding baseline values as covariates. FEV_1 % predicted normal values were derived using Global Lung Function Initiative prediction equations.[28,29] Median adherence and ICS daily dose were summarized for SYGMA 1 and SYGMA 2 separately because of different study designs. BUD and FORM doses are reported as metered doses (for BUD, 200 μg metered dose corresponds to 160 μg delivered dose; for FORM, 6 μg metered dose corresponds to 4.5 μg delivered dose). Change from baseline in height was analyzed overall and by age (≥12 years to <14 years and ≥14 years to 18 years) and sex subgroups. No adjustment was made for multiple comparisons.

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participating in the study.

RESULTS

Patients

The 889 adolescent patients comprising the pooled SYGMA 1 (n = 478 [12.5% of the total population]) and SYGMA 2 populations (n = 411 [10% of the total population]) were randomized to as-needed terbutaline (n = 144; SYGMA 1 only), as-needed BUD-FORM (n = 366), or BUD maintenance (n = 379). Baseline demographics were generally similar between randomization groups in the adolescent populations of SYGMA 1 and SYGMA 2, both pooled and separate (Table I; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Although adolescents were generally well distributed across the age range, slightly more were in the older adolescent category (Table E1).

Severe exacerbations

In SYGMA 1, the annualized rate of severe exacerbations in adolescents was 77% lower with as-needed BUD-FORM versus as-needed terbutaline, (0.04 vs 0.17; rate ratio, 0.23; 95% CI, 0.09 to 0.65; $P = .005$) (Figure 1), and time to first severe exacerbation was significantly longer with as-needed BUD-FORM versus as-needed terbutaline (hazard ratio, 0.33; 95% CI, 0.13 to 0.85; $P = .02$) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

In both SYGMA 1 and SYGMA 2, and in the pooled analysis, the annualized rate of severe exacerbations with as-needed BUD-FORM was similar to that with BUD maintenance, with the severe exacerbation rates in the pooled analysis being 0.08 versus 0.07 per patient per year, respectively (rate ratio, 1.16; 95% CI,

TABLE I. Baseline* demographic and clinical characteristics of adolescent populations: SYGMA 1 and SYGMA 2

Characteristic	SYGMA 1			SYGMA 2	
	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
Overall adolescent population					
No. of patients, n	144	161	173	205	206
Age (y), mean ± SD	13.9 ± 1.6	14.0 ± 1.7	14.0 ± 1.7	14.3 ± 1.8	14.1 ± 1.7
Male sex, n (%)	85 (59.0)	105 (65.2)	110 (63.6)	121 (59.0)	120 (58.3)
Time since asthma diagnosis (y), median (range)	6.28 (0.6-16.2)	7.21 (0.6-16.3)	6.34 (0.5-17.0)	7.33 (0.6-17.6)	7.26 (0.5-16.4)
Prebronchodilator FEV_1 % predicted, mean ± SD	88.57 ± 14.70	90.26 ± 14.41	87.78 ± 13.16	89.47 ± 14.65	89.95 ± 15.11
Reversibility (%), mean ± SD	15.0 ± 11.3	15.1 ± 9.2	14.6 ± 9.1	13.9 ± 12.5	14.5 ± 12.6
Severe exacerbation in the last 12 mo, n (%)	29 (20.1)	46 (28.6)	31 (17.9)	36 (17.6)	46 (22.3)
ACQ-5 score at study entry, mean ± SD	1.32 ± 0.90	1.42 ± 0.95	1.39 ± 1.03	1.35 ± 0.96	1.39 ± 0.94
Pre-study treatment, n (%)					
Uncontrolled on BD†	63 (43.75)	58 (36.02)	87 (50.29)	85 (41.46)	79 (38.35)
Controlled on ICS or LTRA†	81 (56.25)	103 (63.98)	86 (49.71)	120 (58.54)	127 (61.65)

ACQ-5, Asthma Control Questionnaire-5; *BD,* bronchodilator; *BUD-FORM*, budesonide-formoterol; *FEV_1*, forced expiratory volume in 1 second; *ICS,* inhaled corticosteroid; *LTRA*, leukotriene receptor antagonist; *SD*, standard deviation.
*Baseline defined as visit 2 (end of run-in on SABA alone).
†Level of asthma control on pre-study treatment was physician-assessed.

0.64 to 2.10; $P = .634$) (Figure 1), consistent with findings across the entire study populations of SYGMA 1 and 2.[18,19] Time to first severe exacerbation was also not significantly different between as-needed BUD-FORM and BUD maintenance in the pooled analysis (hazard ratio, 1.23; 95% CI, 0.70 to 2.18; $P = .47$) (Figure E1).

Symptom control and lung function

In SYGMA 1, mean ACQ-5 score improved from baseline with both as-needed BUD-FORM (−0.32; 95% CI, −0.42 to −0.22) and with as-needed terbutaline (−0.15; 95% CI, −0.25 to −0.05). The change from baseline in ACQ-5 score was significantly greater with as-needed BUD-FORM compared with as-needed terbutaline (−0.17; 95% CI, −0.30 to −0.03; $P = .02$), but this difference did not reach the minimal clinically important difference of 0.5 (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Mean ACQ-5 score improved from baseline to a similar degree with as-needed BUD-FORM and BUD maintenance in SYGMA 1 and SYGMA 2 (Table E2); in the pooled adolescent population, mean ACQ-5 score improved from baseline with both as-needed BUD-FORM (−0.38; 95% CI, −0.45 to −0.31) and BUD maintenance (−0.44; 95% CI, −0.50 to −0.37), and these changes were not significantly different (mean difference, 0.06; 95% CI, −0.03 to 0.15; $P = .21$) (Table E2).

No statistically significant difference in change in FEV_1 % predicted from baseline between as-needed BUD-FORM and as-needed terbutaline was observed in SYGMA 1 (0.9%; 95% CI, −1.1 to 2.8; $P = .395$) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). A statistically significant difference in change in FEV_1 % predicted from baseline was observed with as-needed BUD-FORM versus BUD maintenance in SYGMA 1 (estimated difference, −3.9%; 95% CI, −5.8 to −1.9; $P < .001$) (Table E3) and in the pooled analysis (estimated difference, −2.3%; 95% CI, −3.7 to −1.0; $P < .001$) (Table E3), but not in SYGMA 2 (Table E3).

Adherence and ICS dose

Adherence by adolescents to blinded randomized maintenance treatment (placebo or BUD) in SYGMA 1 was similar between the as-needed terbutaline, as-needed BUD-FORM, and BUD maintenance groups (median adherence, 73.1%, 72.8%, and 73.1%, respectively; overall, 73.1%). Likewise, in SYGMA 2, adherence with blinded maintenance treatment (placebo or BUD) was similar between the as-needed BUD-FORM and BUD maintenance groups (53.5% and 49.9%, respectively; overall, 51.3%) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

In SYGMA 1, patients used a mean (± standard deviation [SD]) of 0.44 ± 0.61, 0.34 ± 0.39, and 0.31 ± 0.46 inhalations per day of their as-needed inhaler during the treatment period in the as-needed terbutaline, as-needed BUD-FORM, and BUD maintenance groups, corresponding to 3.1, 2.4, and 2.2 inhalations per week, respectively. In SYGMA 2, the respective values were 0.36 ± 0.44 and 0.31 ± 0.51 inhalations per day, corresponding to 2.5 and 2.2 inhalations per week.

In SYGMA 1, median daily BUD dose from randomized treatment was 35.1 μg for adolescents randomized to as-needed

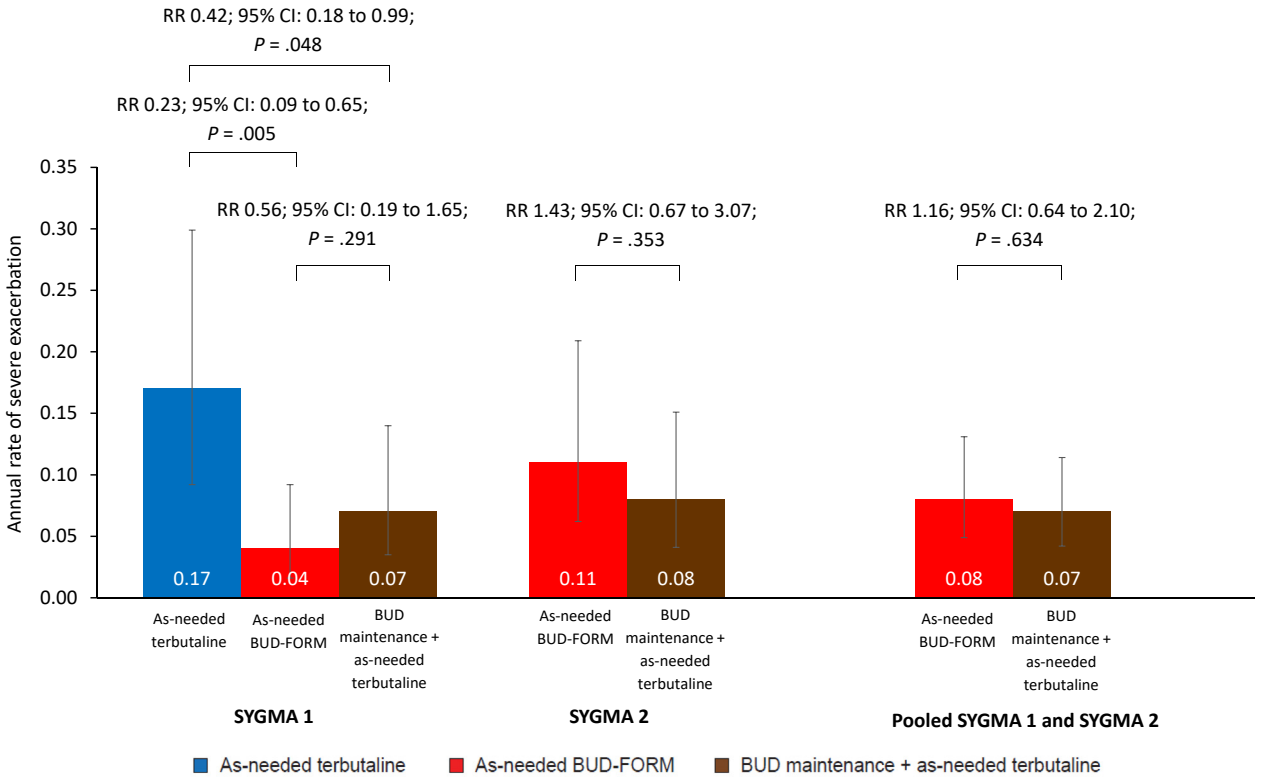

FIGURE 1. Annual severe exacerbation rate by randomized treatment: adolescent populations from SYGMA 1, SYGMA 2, and pooled population from SYGMA 1 and 2. *BUD-FORM*, budesonide-formoterol; *CI*, confidence interval; *RR*, Rate ratio. Annualized rate of severe exacerbations was analyzed in SYGMA 1 and SYGMA 2 using a negative binomial model with randomized treatment, pre-study asthma treatment, and number of severe exacerbations in the previous year (0, ≥1) as factors, and the logarithm of the follow-up time as an offset variable. The same model was used for the analysis of the pooled population, with region and study also included as factors. The absolute numbers of severe exacerbations for each treatment group in SYGMA 1 were 19, 6, and 10 for as-needed terbutaline, as-needed BUD-FORM, and BUD maintenance, respectively. Severe exacerbation numbers were 24 and 17 in SYGMA 2, and 30 and 27 in the pooled population, for as-needed BUD-FORM and BUD maintenance, respectively.

BUD-FORM, compared with 292.2 μg with BUD maintenance plus as-needed terbutaline. In SYGMA 2, the corresponding median daily BUD doses were 42.3 μg and 198.9 μg, respectively (Figure E2).

Change in height

In younger adolescents (aged ≥12 to <14 years), mean change in height from baseline was not significantly different with as-needed BUD-FORM (4.5 cm) compared with as-needed terbutaline (4.1 cm) in the adolescent population of SYGMA 1 ($P = .50$). Mean change in height from baseline was significantly greater with as-needed BUD-FORM compared with BUD maintenance in the pooled analysis (4.8 vs 3.9 cm; $P < .046$) and in SYGMA 2, but not in SYGMA 1 (Table II). In older adolescents (aged ≥14 to <18 years), mean change in height from baseline was similar for as-needed BUD-FORM and as-needed terbutaline in the SYGMA 1 population (1.4 vs 1.3 cm; $P = .975$), and for as-needed BUD-FORM and BUD maintenance in SYGMA 1, SYGMA 2, and the pooled population (1.4 vs 1.4 cm; $P = .912$) (Table II).

In both males and females, mean (± SD) change in height from baseline was greater in those aged ≥12 to <14 years (females, 2.4 ± 2.3 cm; males, 5.4 ± 3.8 cm) versus those aged ≥14 to <18 years (females, 0.7 ± 1.4 cm; males, 1.9 ± 2.7 cm). Across all randomization groups, greater changes in height were observed in males aged ≥12 to <14 years versus females in the same age group.

Adverse events

The proportion of adolescents experiencing any AE was similar between as-needed BUD-FORM and BUD maintenance (33.9% and 33.2%, respectively), but was higher with as-needed terbutaline (41.0%), primarily due to asthma-related events. Severe AEs were also higher with as-needed terbutaline (4.2%) than with as-needed BUD-FORM and BUD maintenance (1.9% and 1.1%, respectively). The difference in the proportion of severe AEs between as-needed BUD-FORM and BUD maintenance was not significant ($P = .316$). The AE profile was consistent with findings across the entire study population in SYGMA 1 and 2.[18,19]

DISCUSSION

This analysis of adolescent patients with mild asthma requiring GINA Step 2 treatment found that in SYGMA 1, as-needed BUD-FORM was associated with a 77% reduction in the severe exacerbation rate (0.04 vs 0.17; rate ratio, 0.23) and

TABLE II. Mean height of adolescents at baseline and 52 wks by age category in the adolescent population of SYGMA 1, the adolescent population of SYGMA 2, and the pooled adolescent population of SYGMA 1 and 2

Population	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
SYGMA 1 population			
Adolescents aged ≥12 to <14 y			
Baseline			
No. of patients, n	72	74	75
Mean ± SD height (cm)	154.9 ± 8.1	157.4 ± 10.4	154.2 ± 9.5
Week 52			
No. of patients, n	63	69	72
Mean ± SD height (cm)	158.8 ± 9.1	161.5 ± 9.6	158.3 ± 9.8
Change from baseline ± SD (cm)	4.1 ± 3.5	4.5 ± 3.5	4.0 ± 3.6
Comparison between as-needed BUD-FORM and comparator, *P* value	.500	—	.439
Adolescents aged ≥14 to <18 y			
Baseline			
No. of patients, n	72	87	98
Mean ± SD height (cm)	167.9 ± 10.1	166.0 ± 9.7	164.8 ± 10.5
Week 52			
No. of patients, n	69	80	81
Mean ± SD height (cm)	169.6 ± 10.1	167.8 ± 9.3	167.2 ± 10.3
Change from baseline ± SD (cm)	1.3 ± 2.4	1.4 ± 2.0	1.7 ± 2.6
Comparison between as-needed BUD-FORM and comparator, *P* value	.975	—	.325
SYGMA 2 population			
Adolescents aged ≥12 to <14 y			
Baseline			
No. of patients, n	—	80	92
Mean ± SD height (cm)	—	154.0 ± 10.4	155.9 ± 7.8
Week 52			
No. of patients, n	—	75	91
Mean ± SD height (cm)	—	158.6 ± 10.5	159.7 ± 8.0
Change from baseline ± SD (cm)	—	5.0 ± 4.4	3.8 ± 3.2
Comparison between as-needed BUD-FORM and comparator (BUD maintenance), *P* value	—	—	.049
Adolescents aged ≥14 to <18 y			
Baseline			
No. of patients, n	—	125	114
Mean ± SD height (cm)	—	163.7 ± 10.4	165.1 ± 9.0
Week 52			
No. of patients, n	—	116	104
Mean ± SD height (cm)	—	164.8 ± 10.5	166.5 ± 9.3
Change from baseline ± SD (cm)	—	1.5 ± 2.4	1.2 ± 2.2
Comparison between as-needed BUD-FORM and comparator (BUD maintenance), *P* value	—	—	.307
Pooled adolescent population			
Adolescents aged ≥12 to <14 y			
Baseline			
No. of patients, n	—	154	167
Mean ± SD height (cm)	—	155.6 ± 10.5	155.1 ± 8.6
Week 52			
No. of patients, n	—	144	163
Mean ± SD height (cm)	—	160.0 ± 10.2	159.1 ± 8.8
Change from baseline ± SD (cm)	—	4.8 ± 4.0	3.9 ± 3.4
Comparison between as-needed BUD-FORM and BUD maintenance, *P* value	—	—	.046

(continued)

TABLE II. *(Continued)*

Population	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
Adolescents aged ≥14 to <18 y			
Baseline			
No. of patients, n	—	212	212
Mean ± SD height (cm)	—	164.6 ± 10.2	164.9 ± 9.7
Week 52			
No. of patients, n	—	196	185
Mean ± SD height (cm)	—	166.0 ± 10.1	166.8 ± 9.7
Change from baseline ± SD (cm)	—	1.4 ± 2.3	1.4 ± 2.4
Comparison between as-needed BUD-FORM and BUD maintenance, *P* value	—	—	.912

BUD-FORM, Budesonide-formoterol; *SD*, standard deviation.
Baseline defined as visit 2 (run-in). Change in height was calculated by subtracting baseline height from end of study height.

significantly longer time to first severe exacerbation versus as-needed SABA. As-needed BUD-FORM had similar efficacy to BUD maintenance plus as-needed SABA for severe exacerbations, with no clinically important difference in symptom control as assessed by ACQ-5 score. Change from baseline in prebronchodilator FEV_1 % predicted was significantly higher with BUD maintenance compared with as-needed BUD-FORM, but the difference was not clinically important. These results with as-needed BUD-FORM were achieved with less than a quarter of the median daily ICS dose compared with BUD maintenance.

As-needed BUD-FORM had a protective effect in adolescents on the annual rate of severe exacerbations and time to first severe exacerbation compared with as-needed SABA, as was also reported for the overall populations of the SYGMA trials.[18,19] This is consistent with findings for adolescents in a pooled analysis of maintenance and reliever therapy studies with low-dose BUD-FORM.[23] Although the adolescent patients in the SYGMA studies were assessed by their physicians as having mild asthma and (unlike in the maintenance and reliever therapy studies) were not required to have had a severe exacerbation in the previous year, asthma is variable in nature and severe exacerbations and even death can still occur in mild asthma[17]; overall, 21% of adolescents randomized in the SYGMA studies had a severe exacerbation in the previous 12 months. The reduced risk of severe exacerbations seen in SYGMA 1 compared with SABA alone may be explained by the fact that as-needed BUD-FORM leverages the inherent relief-seeking behavior of patients to deliver additional doses of the combination inhaler,[30] with both ICS and formoterol known to reduce the overall risk of progression to a severe exacerbation.[31-33] As-needed BUD-FORM in mild asthma also reduces the short-term risk of severe exacerbations after a single day of even modestly high reliever use, compared with as-needed SABA.[34] Furthermore, the reduction in severe exacerbation risk, and hence in exposure to oral corticosteroids (OCS), was similar to that with BUD maintenance, with a lower ICS load and no need for daily treatment. A therapy delivering an overall lower corticosteroid load would be a desirable treatment choice for many patients.

Among other asthma outcomes, there were statistically significant differences in change in symptom control (ACQ-5) between as-needed BUD-FORM and maintenance BUD (in SYGMA 1 only), and between as-needed BUD-FORM and as-needed terbutaline, but the differences were well below the clinically important difference of 0.5. For change in prebronchodilator FEV_1, there was a statistically significant but not clinically relevant (mean, −2.3%) difference between as-needed BUD-FORM and maintenance BUD; thresholds of 5% to 10% have been used as an indication of clinically meaningful changes in FEV_1 in cystic fibrosis trials that included adolescent patients, although these thresholds are themselves well within the inherent variability of the test.[35] The Global Lung Initiative has highlighted that variability in FEV_1 increases during the adolescent growth spurt.[29]

Adherence is well known to be problematic in adolescence,[6-8] and this was confirmed by the present analyses. Median adherence with maintenance treatment was only 73% in SYGMA 1 despite twice-daily electronic reminders, and was even lower (51%) in the more pragmatic SYGMA 2 study, with similar adherence between treatment arms in each study, as expected, due to their double-blind designs. Furthermore, adherence among the adolescent participants was lower compared with that among the overall populations of the SYGMA studies (including adult and adolescent patients), where the median adherence to randomized treatment was 85% to 86% and 67% to 68% for SYGMA 1 and SYGMA 2, respectively.[18,19] Persistence with controller therapy is even lower in clinical practice where there may be less frequent supervision than in a clinical trial; for example, a US study found that 63% of children aged 2 to 17 years discontinued asthma controller treatment within 3 months, and discontinuations were more likely among adolescents than among younger children.[6] Adolescence is a period of substantial physical, emotional, and social change, providing significant challenges for adolescents with chronic health conditions. During this transitional life phase, adolescents often start to take more responsibility for medication self-management,[10,36] but factors including low motivation,[7,37] forgetfulness,[38,39] desire for peer conformity (resulting in feelings of shame or invincibility),[39] perceptions of illness,[37] and cost[6] can contribute to poor adherence. Poor adherence leaves the adolescent exposed to the risks of SABA-only treatment and thus increased risk of exacerbations, and overuse of SABA may also be an issue among adolescents.[9] Of the 2 treatment approaches recommended by GINA for mild asthma (as-needed ICS-formoterol, or maintenance ICS with as-needed SABA),[21] the latter is the more

vulnerable to such risks because when patients are nonadherent with maintenance ICS, their only treatment becomes SABA, with no anti-inflammatory treatment, whereas as-needed ICS-formoterol provides both symptom relief and protection from exacerbations, and the risk of reliever overuse is less than with SABA.[18,19]

Another option described in the GINA report, but with less evidence for efficacy and safety, is for the patient to take a dose of ICS whenever they use their SABA inhaler. This regimen has been evaluated among children and adolescents in 2 studies,[40,41] with one (n = 288) showing a trend to fewer severe exacerbations compared with SABA alone,[40] and the other, a pragmatic study in Black children (n = 206), finding similar symptom control as with physician-adjusted treatment.[41] Data for adolescents (for whom carrying 2 inhalers may be more of a problem) have not yet been reported separately.

In the management of adolescent patients with asthma, shared decision making is becoming increasingly important to identify and address parental and patient concerns about asthma and its treatment.[42] One factor that may contribute to poor adherence during adolescence is the widespread perception that regular ICS may "stunt" growth. Among children aged 11 to 15 years at baseline in the inhaled Steroid Treatment As Regular Therapy in early asthma study, regular maintenance BUD 400 μg/d was associated with lower growth versus placebo of 0.40 cm/y (95% CI, −0.66 to −0.14).[43] However, any effect of regular treatment appears to occur predominantly in the first 12 months, and in the childhood asthma management program study, the only randomized controlled trial to have followed children through to adult life, there was no difference in adult height among those who had entered the study at ages 9 to 13 years if they had been randomized to BUD versus placebo for the 4- to 6-year study duration.[44] Furthermore, poorly controlled asthma is associated with reduced growth, with a potential contribution from OCS use.[12] The present findings from the SYGMA studies found no evidence of growth suppression in adolescents randomized to as-needed BUD-FORM, with mean increase in height from baseline numerically greater than with either as-needed SABA or maintenance BUD during the period of maximum growth. The only previous data on growth with symptom-based use of ICS in mild asthma are from the TREXA study in children aged 5 to 18 years, which showed a significant difference in growth over 10 months in the 2 groups randomized to receive maintenance low-dose beclometasone, but no significant difference in growth in the group receiving ICS whenever they took their SABA inhaler, or SABA alone.[40]

Strengths of the present analysis include the population of almost 900 adolescents, almost half of whom were younger than 14 years, which contrasts with many clinical trials in which adolescents are often predominantly aged 16 to 17 years. Further strengths included the 12-month duration of both studies and the electronic recording of all randomized medication use, allowing accurate data for adherence. Limitations include that this is a *post hoc* pooled subgroup analysis, and that for regulatory purposes, both SYGMA studies were double-blind, with all patients required to take a twice-daily placebo inhaler. The 2 subsequent open-label studies of as-needed BUD-FORM in mild asthma were limited to adults,[24,25] so the present analysis provides the only data for as-needed ICS-formoterol in adolescents with mild asthma.

CONCLUSIONS

Our findings provide evidence that reliever therapy with as-needed BUD-FORM is a safe and effective treatment option in adolescent patients with mild asthma, substantially reducing the risk of severe exacerbations and hence the need for OCS treatment compared with SABA alone, with similar levels of symptom control and lung function as with maintenance ICS. Given the as-needed nature of this treatment, the well-documented challenges with adherence and with reliance on SABA alone in the adolescent population may be avoided if patients can receive the protection of ICS without being required to take a daily maintenance treatment.

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TABLE E1. Baseline* demographic and clinical characteristics: Pooled adolescent population, SYGMA 1, and SYGMA 2

Characteristic	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
Overall pooled adolescent population			
No. of patients, n	—	366	379
Age (y), mean ± SD	—	14.2 ± 1.7	14.1 ± 1.7
Male sex, n (%)	—	226 (61.7)	230 (60.7)
Time since asthma diagnosis (y), median (range)	—	7.3 (0.6-17.6)	6.6 (0.5-17.0)
Prebronchodilator FEV_1 % predicted, mean ± SD	—	89.8 ± 14.5	89.0 ± 14.3
Reversibility (%), mean ± SD	—	14.5 ± 11.1	14.6 ± 11.2
Severe exacerbation in the last 12 mo, n (%)	—	82 (22.4)	77 (20.3)
ACQ-5 score at study entry, mean ± SD	—	1.4 ± 1.0	1.4 ± 1.0
Pre-study treatment, n (%)			
Uncontrolled on BD†	—	143 (39.1)	166 (43.8)
Controlled on ICS or LTRA†	—	223 (60.9)	213 (56.2)
Pooled population: Adolescents aged 12 to <14 y			
No. of patients, n	—	154	167
Age (y), mean ± SD	—	12.4 ± 0.5	12.4 ± 0.5
Male sex, n (%)	—	102 (66.2)	105 (62.9)
Time since asthma diagnosis (y), median (range)	—	5.96 (0.6-13.2)	5.61 (0.5-13.4)
Prebronchodilator FEV_1 % predicted, mean ± SD	—	91.61 ± 14.87	90.20 ± 14.43
Reversibility (%), mean ± SD	—	14.4 ± 12.6	15.2 ± 12.8
Severe exacerbation in the last 12 mo, n (%)	—	28 (18.2)	34 (20.4)
ACQ-5 score at study entry, mean ± SD	—	1.23 ± 0.92	1.31 ± 0.98
Pre-study treatment, n (%)			
Uncontrolled on BD†	—	49 (31.82)	69 (41.32)
Controlled on ICS or LTRA†	—	105 (68.18)	98 (58.68)
Pooled population: Adolescents aged ≥14 to <18 y			
No. of patients, n	—	212	212
Age (y), mean ± SD	—	15.4 ± 1.1	15.4 ± 1.1
Male sex, n (%)	—	124 (58.5)	125 (59.0)
Time since asthma diagnosis (y), median (range)	—	7.77 (0.6-17.6)	8.29 (0.5-17.0)
Prebronchodilator FEV_1 % predicted, mean ± SD	—	88.52 ± 14.17	87.98 ± 14.11
Reversibility (%), mean ± SD	—	14.5 ± 10.0	14.1 ± 9.6
Severe exacerbation in the last 12 mo, n (%)	—	54 (25.5)	43 (20.3)
ACQ-5 score at study entry, mean ± SD	—	1.49 ± 0.97	1.45 ± 0.99
Pre-study treatment, n (%)			
Uncontrolled on BD†	—	94 (44.34)	97 (45.75)
Controlled on ICS or LTRA†	—	118 (55.66)	115 (54.25)
SYGMA 1: Adolescents aged 12 to <14 y			
No. of patients, n	72	74	75
Age (y), mean ± SD	12.5 ± 0.5	12.4 ± 0.5	12.3 ± 0.5
Male sex, n (%)	39 (54.2)	50 (67.6)	51 (68.0)
Time since asthma diagnosis (y), median (range)	5.60 (0.6-12.4)	7.66 (0.6-13.2)	5.00 (0.5-12.5)
Prebronchodilator FEV_1 % predicted, mean ± SD	90.7 (15.43)	91.33 (14.16)	88.98 (13.18)
Reversibility (%), mean ± SD	14.9 ± 10.8	15.5 ± 9.2	15.0 ± 11.3
Severe exacerbation in the last 12 mo, n (%)	12 (16.7)	17 (23.0)	14 (18.7)
ACQ-5 score at study entry, mean ± SD	1.26 ± 0.92	1.37 ± 0.96	1.31 ± 1.07
Pre-study treatment, n (%)			
Uncontrolled on BD†	33 (45.83)	26 (35.14)	34 (45.33)
Controlled on ICS or LTRA†	39 (54.17)	48 (64.86)	41 (54.67)
SYGMA 1: Adolescents aged ≥14 to <18 y			
No. of patients, n	72	87	98

(continued)

TABLE E1. *(Continued)*

Characteristic	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
Age (y), mean ± SD	15.3 ± 1.1	15.3 ± 1.0	15.3 ± 1.0
Male sex, n (%)	46 (63.9)	55 (63.2)	59 (60.2)
Time since asthma diagnosis (y), median (range)	7.26 (0.6-16.2)	6.51 (0.6-16.3)	7.60 (0.5-17.0)
Prebronchodilator FEV_1 % predicted, mean ± SD	87.06 ± 13.88	89.34 ± 14.64	86.87 ± 13.14
Reversibility (%), mean ± SD	15.1 ± 11.8	14.8 ± 9.3	14.4 ± 7.1
Severe exacerbation in the last 12 mo, n (%)	17 (23.6)	29 (33.3)	17 (17.3)
ACQ-5 score at study entry, mean ± SD	1.39 ± 0.88	1.46 ± 0.95	1.46 ± 1.01
Pre-study treatment, n (%)			
Uncontrolled on BD†	30 (41.67)	32 (36.78)	53 (54.08)
Controlled on ICS or LTRA†	42 (58.33)	55 (63.22)	45 (45.92)
SYGMA 2: Adolescents aged 12 to <14 y			
No. of patients, n	—	80	92
Age (y), mean ± SD	—	12.4 ± 0.5	12.5 ± 0.5
Male sex, n (%)	—	52 (65.0)	54 (58.7)
Time since asthma diagnosis (y), median (range)	—	5.41 (1.0-12.9)	6.14 (0.5-13.4)
Prebronchodilator FEV_1 % predicted, mean ± SD	—	91.88 ± 15.61	91.20 ± 15.38
Reversibility (%), mean ± SD		13.4 ± 15.1	15.3 ± 14.1
Severe exacerbation in the last 12 mo, n (%)	—	11 (13.8)	20 (21.7)
ACQ-5 score at study entry, mean ± SD	—	1.11 ± 0.88	1.31 ± 0.91
Pre-study treatment, n (%)			
Uncontrolled on BD†	—	23 (28.75)	35 (38.04)
Controlled on ICS or LTRA†	—	57 (71.25)	57 (61.96)
SYGMA 2: Adolescents aged ≥14 to <18 y			
No. of patients, n	—	125	114
Age (y), mean ± SD	—	15.5 ± 1.1	15.4 ± 1.1
Male sex, n (%)	—	69 (55.2)	66 (57.9)
Time since asthma diagnosis (y), median (range)	—	8.97 (0.6-17.6)	8.84 (0.5-16.4)
Prebronchodilator FEV_1 % predicted, mean ± SD	—	87.95 ± 13.86	88.94 ± 14.89
Reversibility (%), mean ± SD	—	14.2 ± 10.5	13.8 ± 11.4
Severe exacerbation in the last 12 mo, n (%)	—	25 (20.0)	26 (22.8)
ACQ-5 score at study entry, mean ± SD	—	1.51 ± 0.98	1.45 ± 0.97
Pre-study treatment, n (%)			
Uncontrolled on BD†	—	62 (49.6)	44 (38.6)
Controlled on ICS or LTRA†	—	63 (50.4)	70 (61.4)

ACQ-5, Asthma Control Questionnaire-5; *BD*, bronchodilator; *BUD-FORM*, budesonide-formoterol; *FEV_1*, forced expiratory volume in 1 second; *ICS,* inhaled corticosteroid; *LTRA*, leukotriene receptor antagonist; *SD*, standard deviation.

*Baseline defined as visit 2 (end of run-in).

†Level of asthma control on pre-study treatment was physician-assessed.

TABLE E2. Change from baseline in ACQ-5 score in the adolescent population of SYGMA 1, the adolescent population of SYGMA 2, and the pooled adolescent population

Population	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
SYGMA 1 population*			
No. of patients, n	143	160	167
Baseline ACQ-5 score, mean ± SD	1.31 ± 0.92	1.42 ± 0.99	1.37 ± 0.94
Change from baseline to treatment average (95% CI)	−0.15 (−0.25 to −0.05)	−0.32 (−0.42 to −0.22)	−0.46 (−0.55 to −0.36)
Comparison between as-needed BUD-FORM and comparator			
Estimate for difference	−0.167	—	0.134
95% CI	−0.30 to −0.03	—	0.00 to 0.27
P value	.017	—	.047
SYGMA 2 population*			
No. of patients, n	—	196	197
Baseline ACQ-5 score, mean ± SD	—	1.30 ± 0.85	1.40 ± 0.91
Change from baseline to treatment average (95% CI)	—	−0.45 (−0.54 to −0.36)	−0.44 (−0.53 to −0.35)
Comparison between as-needed BUD-FORM and BUD maintenance			
Estimate for difference	—	—	−0.01
95% CI	—	—	−0.13 to 0.11
P value	—	—	.882
Pooled adolescent population†			
No. of patients, n	—	356	364
Baseline ACQ-5 score, mean ± SD	—	1.35 ± 0.92	1.39 ± 0.92
Change from baseline to treatment average (95% CI)	—	−0.38 (−0.45 to −0.31)	−0.44 (−0.50 to −0.37)
Comparison between as-needed BUD-FORM and BUD maintenance			
Estimate for difference	—	—	0.06
95% CI	—	—	−0.03 to 0.15
P value	—	—	.211

ACQ-5, Asthma Control Questionnaire-5; *BUD-FORM*, budesonide-formoterol; *CI,* confidence interval; *SD,* standard deviation.
The minimal clinically important difference for ACQ-5 is 0.5.
*Changes from baseline in ACQ-5 scores were analyzed on the basis of a mixed model for repeated measures, with randomized treatment, pre-study asthma treatment, region, visit, and randomized treatment-by-visit interaction as fixed effects, baseline values as a covariate, and subject as a random effect in the adolescent population of SYGMA 1 and SYGMA 2.
†Changes from baseline in ACQ-5 scores were analyzed by an analysis of covariance model, with randomized treatment, pre-study asthma treatment, region, and study as factors, and the corresponding baseline values as covariates in the pooled adolescent population.

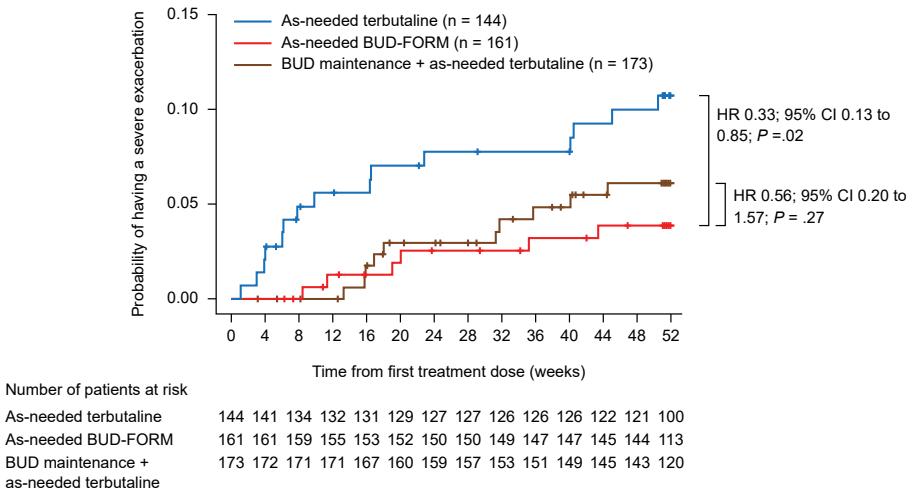
TABLE E3. Change from baseline in FEV_1 % predicted in the adolescent population of SYGMA 1, the adolescent population of SYGMA 2, and the pooled adolescent population

Population	As-needed terbutaline	As-needed BUD-FORM	BUD maintenance + as-needed terbutaline
SYGMA 1 population*			
No. of patients, n	143	161	172
Baseline prebronchodilator FEV_1 % predicted, mean ± SD	88.57 ± 14.70	90.26 ± 14.41	87.78 ± 13.16
Change from baseline to treatment average (95% CI)	1.5 (0.0 to 2.9)	2.4 (1.0 to 3.8)	6.2 (4.9 to 7.5)
Comparison between as-needed BUD-FORM and comparator			
Estimate for difference	0.9	—	−3.9
95% CI	−1.1 to 2.8	—	−5.8 to −1.9
P value	.395	—	<.001
SYGMA 2 population*			
No. of patients, n	—	198	203
Baseline prebronchodilator FEV_1 % predicted, mean ± SD	—	89.47 ± 14.65	89.95 ± 15.11
Change from baseline to treatment average (95% CI)	—	1.8 (0.4 to 3.1)	3.2 (1.9 to 4.6)
Comparison between as-needed BUD-FORM and BUD maintenance			
Estimate for difference	—	—	−1.5
95% CI	—	—	−3.3 to 0.4
P value	—	—	.116
Pooled adolescent population†			
No. of patients, n	—	359	375
Baseline prebronchodilator FEV_1 % predicted, mean ± SD	—	89.82 ± 14.53	88.96 ± 14.28
Change from baseline to treatment average (95% CI)	—	2.1 (1.2 to 3.1)	4.5 (3.5 to 5.4)
Comparison between as-needed BUD-FORM and BUD maintenance			
Estimate for difference	—	—	−2.3
95% CI	—	—	−3.7 to −1.0
P value	—	—	<.001

BUD-FORM, Budesonide-formoterol; *CI*, confidence interval; *SD*, standard deviation.

*Changes from baseline in % predicted FEV_1 were analyzed on the basis of a mixed model for repeated measures, with randomized treatment, pre-study asthma treatment, region, visit, and randomized treatment-by-visit interaction as fixed effects, baseline values as a covariate, and subject as a random effect in the adolescent population of SYGMA 1 and SYGMA 2.

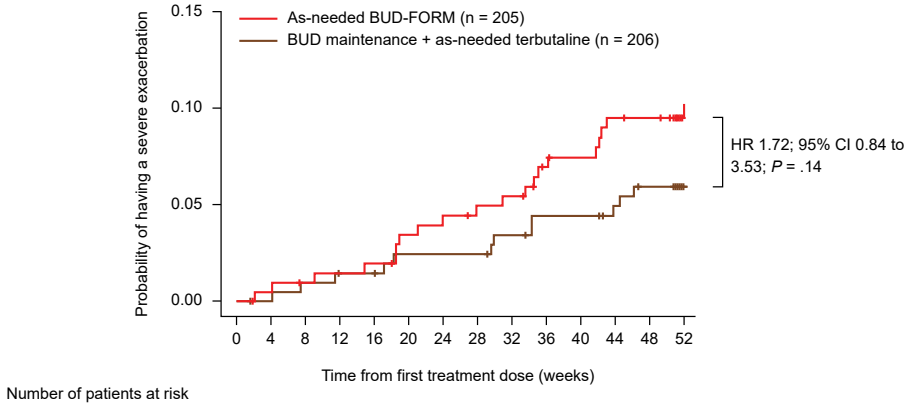
†Changes from baseline in % predicted FEV_1 were analyzed by an analysis of covariance model with randomized treatment, pre-study asthma treatment, region, and study as factors, and the corresponding baseline values as covariates in the pooled adolescent population.



Number of patients at risk

As-needed terbutaline	144	141	134	132	131	129	127	127	126	126	126	122	121	100
As-needed BUD-FORM	161	161	159	155	153	152	150	150	149	147	147	145	144	113
BUD maintenance + as-needed terbutaline	173	172	171	171	167	160	159	157	153	151	149	145	143	120

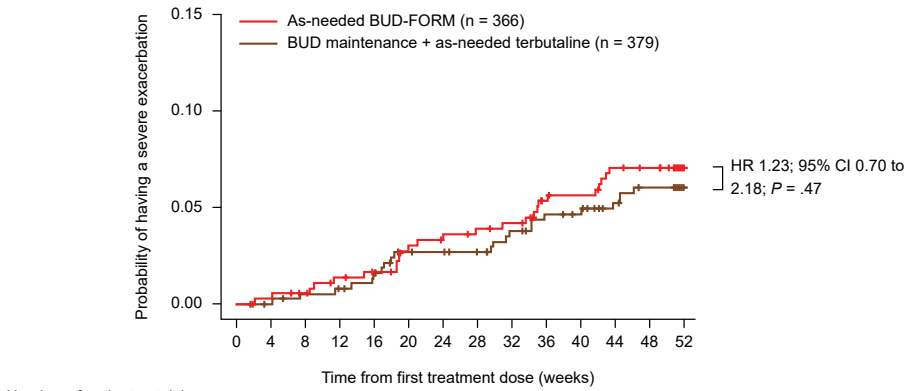
A



Number of patients at risk

As-needed BUD-FORM	205	203	201	200	199	194	193	190	189	182	180	176	175	126
BUD maintenance + as-needed terbutaline	206	205	203	201	201	198	198	198	195	192	192	189	186	142

B



Number of patients at risk

As-needed BUD-FORM	366	364	360	355	352	346	343	340	338	329	327	321	319	239
BUD maintenance + as-needed terbutaline	379	377	374	372	368	358	357	355	348	343	341	334	329	262

C

FIGURE E1. Kaplan-Meier plot for time to first severe exacerbation in (**A**) the adolescent population in SYGMA 1, (**B**) the adolescent population in SYGMA 2, and (**C**) the pooled adolescent population in SYGMA 1 and 2. *BUD-FORM*, budesonide-formoterol; *CI*, confidence interval; *HR*, Hazard ratio. HRs for the analysis of time to first severe exacerbation in SYGMA 1 and SYGMA 2 were derived using a Cox regression model, with randomized treatment, pre-study asthma treatment, and severe exacerbations in the last 12 months (0, ≥1) as covariates. The same model was used for the analysis of the pooled population, with region and study also included as covariates.

	SYGMA 1			SYGMA 2	
	As-needed terbutaline (n = 144)	As-needed BUD-FORM (n = 161)	BUD maintenance + as-needed terbutaline (n = 173)	As-needed BUD-FORM (n = 205)	BUD maintenance + as-needed terbutaline (n = 206)
Daily ICS dose from randomized treatment (μg), median (IQR)	NA	35.1 (9.3-91.6)	292.2 (193.6-341.9)	42.3 (10.4-104.7)	198.9 (127.0-285.8)
Total daily ICS dose, randomized treatment plus open-label ICS (μg), median (IQR)	NA	40.0 (11.0-95.6)	294.2 (194.0-348.4)	42.3 (10.4-104.7)	198.9 (127.0-285.8)

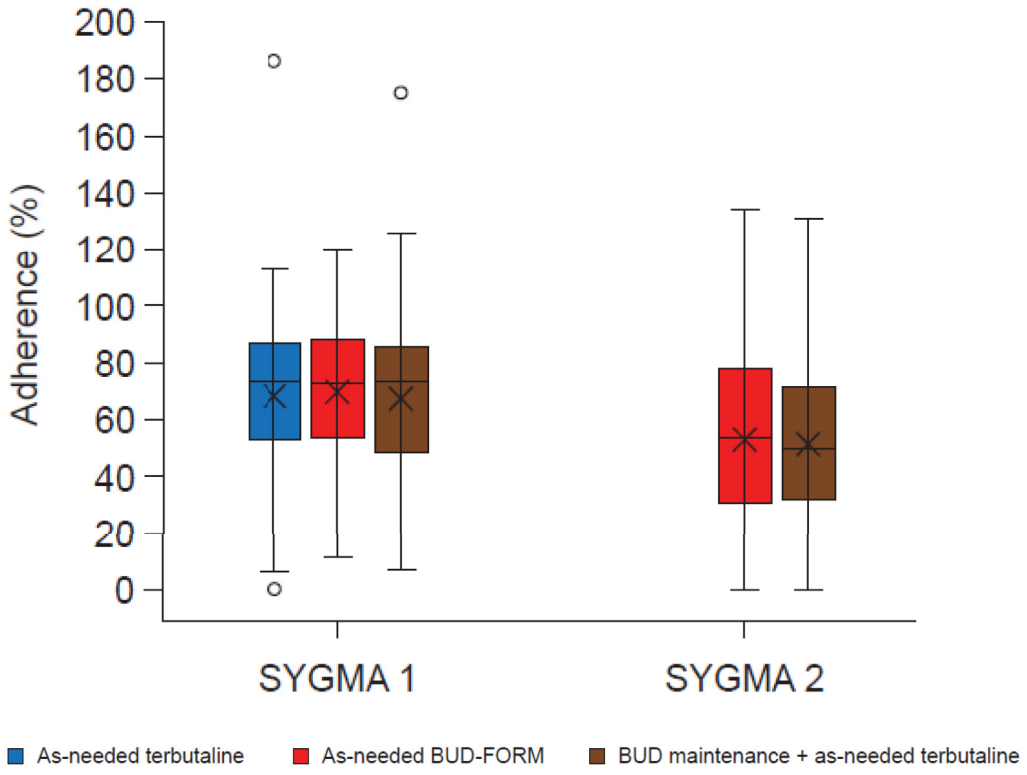


FIGURE E2. Daily ICS dose (μg) and adherence to blinded maintenance treatment during the randomized treatment period in adolescent patients from the SYGMA 1 and 2 trials. *BUD-FORM*, budesonide-formoterol; *ICS*, inhaled corticosteroid; *IQR*, Interquartile range. Inhalations of randomized treatment were collected from Turbuhaler usage electronic monitoring devices. Prescribed additional ICS was recorded via the eCRF. ICS doses are presented as metered dose. Daily ICS dose (from randomized treatment) was calculated by summing the cumulative metered doses (200 μg) of maintenance BUD in the BUD maintenance group and of the BUD in the as-needed BUD-FORM group. Total daily ICS dose (randomized treatment plus open-label ICS) was calculated by summing the randomized treatment dose with total additional ICS. In SYGMA 2, no additional open-label ICS was given; hence, the identical results in the 2 rows. Adherence to maintenance treatment (%): (total actual maintenance inhalations/total expected maintenance inhalations) × 100. The box represents the IQR, and the cross represents the mean. The horizontal line in the box represents the median. Whiskers represent the maximum value within 1.5 × IQR measured from Q1 or Q3, respectively. All observations outside 1.5 × IQR are plotted individually. The median adherence was 73.1% for SYGMA 1 and 51.3% for SYGMA 2.