Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma

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The efficacy/safety of BUD/FORM MART in adolescents with persistent asthma is consistent with that reported in adults http://ow.ly/UYLv30fGDPF

Cite this article as: Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J* 2018; 51: 1701688 [https://doi.org/10.1183/13993003.01688-2017].

ABSTRACT Asthma control is often suboptimal in adolescents, but few studies have evaluated asthma treatments in this population.

This *post hoc* analysis assessed the efficacy and safety of budesonide/formoterol (BUD/FORM) maintenance and reliever therapy (MART) for treatment of persistent asthma in adolescent (age 12–17 years) subgroups within six randomised, double-blind trials. The primary end-point was time to first severe exacerbation. Secondary end-points included number of severe exacerbations, asthma-related symptoms, night-time awakenings, morning peak expiratory flow, forced expiratory volume in 1 s, as-needed medication use and five-item asthma control questionnaire scores.

In adolescents (n=1847), BUD/FORM MART was similar to or more effective than comparators across each of the studies in reducing the risk of a first severe exacerbation (hazard ratios (HR) BUD/FORM MART *versus* comparators 0.15–1.01; pooled HR 0.49, 95% CI 0.34–0.70), with comparable outcomes to the adult subgroups (n=12 197). Similar treatment benefits for BUD/FORM MART were observed for secondary end-points. As-needed medication use was lower with BUD/FORM MART than comparators, and BUD/FORM as-needed use was lower in adolescents than adults. Treatment was well tolerated.

This analysis supports the use of BUD/FORM MART in adolescents with persistent asthma, its efficacy and safety being consistent with that reported for adults.

This article has supplementary material available from erj.ersjournals.com

Received: Aug 18 2017 | Accepted after revision: Sept 30 2017

Support statement: AstraZeneca (the sponsoring company for the studies) developed the analysis plan for this *post hoc* analysis, and funded and carried out the analysis. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Introduction

Adolescence is a period of rapid changes in physical, emotional, cognitive and life circumstances. These changes contribute to the unique challenges of managing asthma in this age group, and therefore adolescents with asthma represent a distinct patient group [1]. In adolescents, asthma control is often suboptimal and morbidity high [2–5], and adherence to regular inhaled therapy (a potential issue in all age groups [6, 7]) can be particularly poor [5, 8]. Despite this, few studies have evaluated the efficacy of treatments in this particular population.

The Global Initiative for Asthma (GINA) guidelines propose a stepwise approach to asthma management, with maintenance and reliever therapy (MART) with an inhaled corticosteroid (ICS)/formoterol (FORM) combination a recommended option at steps 3–5 for both adults and adolescents [1]. Budesonide/formoterol (BUD/FORM) MART provides a low daily maintenance dose of the combination therapy plus additional inhalations as required. Compared with fixed-dose maintenance therapy plus separate reliever medication, the use of BUD/FORM MART ensures that any increase in reliever use in response to worsening symptoms is matched by an increase in ICS, ensuring that inflammation is targeted when symptoms increase [9]. In double-blind randomised controlled trials in patients aged ⩾12 years with asthma, BUD/FORM MART significantly reduced severe exacerbations when compared with ICS/long-acting β_2-agonist (LABA) maintenance (or high-dose ICS) plus short-acting β_2-agonist (SABA) in patients with persistent asthma, while achieving at least similar levels of asthma control [10–15].

At present, limited data have been published evaluating ICS/LABA regimens specifically in adolescents. This *post hoc* individual patient-level analysis was conducted to assess the efficacy and safety of BUD/FORM MART in adolescents (aged 12–17 years) recruited into randomised double-blind controlled trials evaluating this regimen for the treatment of persistent asthma.

Methods

Data sources and study selection

Studies eligible for inclusion were any randomised, double-blind trial comparing BUD/FORM MART with an active comparator in patients with persistent asthma, that were ⩾6 months in duration and which included patients aged 12–18 years. This individual patient-level analysis was conducted for a regulatory dossier on Symbicort MART (SMART) submitted to the European Medicines Agency by the manufacturer (AstraZeneca) to extend the licensed indication for the regimen in Europe to include patients aged ⩾12 years. As such, the data source for the analysis was the AstraZeneca clinical trials database, and included studies completed by November 2015.

To identify whether there were any non-AstraZeneca trials that met the inclusion criteria a separate search of the PubMed database and the Cochrane database was conducted (online supplementary material).

Seven studies that met the criteria were identified in the AstraZeneca clinical trial database: SD-039–0667 (STEAM) [10], SD-039-0668 (STEP) [11], SD-039-0673 (STAY) [12], SD-039-0734 (SMILE) [13], SD-039-0735 (COMPASS) [14], NCT00242775 (AHEAD) [15] and NCT00839800 (SAKURA) [16]. Of these, six were included in the analysis: NCT00839800 was excluded since it randomised only 21 adolescents, all of whom were aged ⩾16 years. No additional studies were identified from the searches of the PubMed and Cochrane databases.

Individual study designs

Detailed methodology and results for each of the studies have been published previously [10–15]. All studies included patients aged ⩾12 years, with a diagnosis of persistent asthma (European Respiratory Society/American Thoracic Society definition [17]) for >6 months and who were symptomatic despite daily ICS use during the study run-in period. Five studies required patients to have one or more asthma exacerbations in the previous year [10, 11, 13–15]. Individual study entry criteria are summarised in online supplementary table S1. Children (aged 4–11 years) were included in one of the studies [12], but are not included in the analyses presented here.

Each study included a 2-week run-in period, during which patients received either their usual ICS dose [11, 12, 14, 15], BUD/FORM (Symbicort; AstraZeneca, Gothenburg, Sweden) 160/4.5 µg twice daily [13] or BUD 200 $\mu g \cdot day^{-1}$ [10] as controller medication. Patients considered not well controlled on the run-in medication (for criteria see online supplementary table S1) were then randomised to BUD/FORM MART or conventional fixed-dose maintenance therapy plus additional reliever therapy (table 1). The comparators, BUD (Pulmicort; AstraZeneca), FORM (Oxis; AstraZeneca) and terbutaline (Bricanyl; AstraZeneca) were administered *via* Turbohaler devices identical to those used for BUD/FORM; salmeterol/fluticasone (Seretide; GlaxoSmithKline, Brentford, UK) was administered *via* Evohaler [14] or

Diskus [15]. Treatment duration was 6 months in three studies [10, 14, 15] and 12 months in the remainder of the trials [11–13].

All studies were conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines, and approved by independent ethics committees. Written consent was obtained from all patients and from parents or guardians of adolescents.

Data extraction and end-points

Individual patient-level data were obtained from the AstraZeneca clinical trial database.

The primary efficacy end-point for this analysis was time to first severe exacerbation, defined as the need for oral corticosteroid (OCS) for ⩾3 days [13–15] and/or hospitalisation/emergency room care due to asthma worsening (online supplementary material). Time to first severe exacerbation was chosen since it was the primary end-point in five of the six studies [11–15]; one study [10] recruited a population with relatively milder disease and hence included peak expiratory flow (PEF) as its primary end-point.

Secondary efficacy end-points included total number of severe exacerbations, changes in asthma-related symptoms, night-time awakenings, morning PEF, forced expiratory volume in 1 s (FEV_1) at clinic visits, use of as-needed medication and five-item asthma control questionnaire (ACQ-5) scores (measured in three studies only [13–15]). Total asthma symptom score was based on patient diary entries, completed twice daily to give a daytime and a night-time score, each graded 0–3 (0: no symptoms, 3: preventing normal activities or sleep), for a total daily score of 0–6. This end-point was not initially part of the analysis, but replaced daytime asthma symptom score after an initial clinical review since it was felt that night-time asthma symptom burden would only partially be captured by night-time awakenings.

Safety was assessed by type and incidence of adverse event.

Statistical methods

All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

TABLE 1 Studies included in the analysis

First author (study code) [ref.]	Duration months	BUD/FORM MART dosing regimen	Comparator(s)	Subjects[#]
Rabe (SD-039-0667) [10]	6	BUD/FORM 80/4.5 µg, 2 inhalations once daily + as needed	BUD 160 µg, 2 inhalations once daily + terbutaline 0.4 mg as needed	Adults 588 (84) Adolescents 109 (16)
Scicchitano (SD-039-0668) [11]	12	BUD/FORM 160/4.5 µg, 2 inhalations once daily + as needed	BUD 160 µg, 2 inhalations twice daily + terbutaline 0.4 mg as needed	Adults 1769 (94) Adolescents 121 (6)
O'Byrne (SD-039-0673) [12] ¶	12	BUD/FORM 80/4.5 µg, 1 inhalation twice daily + as needed	BUD/FORM 80/4.5 µg, 1 inhalation twice daily + terbutaline 0.4 mg as needed or BUD 320 µg, 1 inhalation twice daily + terbutaline 0.4 mg as needed	Adults 2103 (76) Adolescents 316 (12)
Rabe (SD-039-0734) [13]	12	BUD/FORM 160/4.5 µg, 1 inhalation twice daily + as needed	BUD/FORM 160/4.5 µg, 1 inhalation twice daily + FORM 4.5 µg as needed or BUD/FORM 160/4.5 µg, 1 inhalation twice daily + terbutaline 0.4 mg as needed	Adults 3040 (90) Adolescents 354 (10)
Kuna (SD-039-0735) [14]	6	BUD/FORM 160/4.5 µg, 1 inhalation twice daily + as needed	BUD/FORM 320/9 µg, 1 inhalation twice daily + terbutaline 0.4 mg as needed or Salmeterol/fluticasone 25/125 µg, 2 inhalations twice daily + terbutaline 0.4 mg as needed	Adults 2712 (81) Adolescents 623 (19)
Bousquet (NCT00242775) [15]	6	BUD/FORM 160/4.5 µg, 2 inhalations twice daily + as needed	Salmeterol/fluticasone 50/500 µg, 1 inhalation twice daily + terbutaline 0.4 mg as needed	Adults 1985 (86) Adolescents 324 (14)

Data are presented as n or n (%), unless otherwise stated. BUD/FORM: budesonide/formoterol; MART: maintenance and reliever therapy. [#]: adults defined as aged ⩾18 years; adolescents defined as aged 12–17 years (including four 11-year-olds: n=1 in Rabe *et al.* [10], n=1 in Scicchitano *et al.* [11] and n=2 in Kuna *et al.* [14]); [¶]: children (aged 4–11 years; n=341) were recruited in this study [12], but were not included in the current analysis.

Within-study subgroup analyses

Statistical analyses were conducted on the adolescent (12–17 years) subgroup within each study. Additional analyses were performed for the adult (⩾18 years) subgroups within each study, to assess whether the effect observed in adolescents was consistent with that in adults. Due to the relatively small number of patients/events in the adolescent subgroups, it was anticipated that there would be insufficient power to show a statistically significant difference between treatment arms in the adolescent subgroup analyses for the individual studies. Similarly, statistical interaction tests comparing the treatment effects between the adolescent and adult subgroups were not conducted, given the anticipated low power. All statistical analyses were prespecified, unless otherwise stated, and where possible consistent with those planned in the original studies. Since the number of patients/events was generally small in the adolescent subsets, adjusting or stratifying for the effect of country was not always appropriate. Adult subsets were analysed in the same way as the adolescent subsets to ensure comparability. All hypothesis testing was conducted using two-sided alternative hypotheses; p-values of <5% were considered statistically significant, with no correction for multiple testing.

The full analysis set [18] was used in all efficacy analyses, *i.e.* all randomised adolescent and adult patients with data after randomisation. The primary end-point, time to first severe exacerbation, was analysed using Cox regression. The total number of severe exacerbations was analysed using Poisson regression with the natural logarithm of time on study as an offset and including a dispersion parameter. For prebronchodilator FEV_1 and ACQ-5, the change between randomisation visit and the mean value over all remaining follow-up visits was analysed using linear regression, adjusting for the randomisation visit value. Total asthma symptom scores, percentage of night-time awakenings, number of as-needed inhalations and morning PEF were analysed using linear regression with the change between mean value during the run-in period (*i.e.* mean value over 10 days before randomisation) and mean value over the treatment period (excluding day of randomisation) as an outcome variable and adjusting for the run-in period mean value.

Individual patient data subgroup meta-analyses

In addition to the prespecified within-study analyses, the individual patient data were pooled across studies and an overall "BUD/FORM *versus* comparator" estimate was obtained for each of the end-points, separately for adults and adolescents. These pooled or "meta" individual patient data analyses used the same methods outlined previously for each end-point, except with adjustments for study and country, where possible. Time to first severe exacerbation analyses included study as a stratification variable and country as a covariate. For the total number of severe exacerbations, study was included as a covariate, but it was not possible to include country due to convergence issues. The remaining pooled analyses included both study and country as covariates.

The pooled treatment estimates should be interpreted cautiously given the variations between studies. Formal statistical tests of heterogeneity of within subgroup treatment effects across studies were conducted by adding a study-by-treatment interaction term to each pooled subgroup analysis model and comparing the relevant models using a likelihood ratio test [19].

Safety analyses

Safety data were pooled to increase sensitivity to rare events, grouped into three treatment pools: BUD/FORM MART *versus* BUD plus terbutaline as needed [10–12]; BUD/FORM MART *versus* BUD/FORM plus terbutaline as needed [12–14]; and BUD/FORM MART *versus* salmeterol/fluticasone plus terbutaline as needed [14, 15]. A separate safety analysis was conducted for one study [15] in which patients received a higher maintenance dose of BUD/FORM MART than in the other studies (2×160/4.5 μg twice daily).

Role of the funding source

AstraZeneca (the sponsoring company for the studies) developed the analysis plan for this *post hoc* analysis, and funded and performed the analysis. The manuscript was developed by the authors, with the assistance of a medical writer, funded by AstraZeneca.

Results

Patients

1847 adolescents from six studies were randomised to BUD/FORM MART (n=694); BUD plus terbutaline (n=225); BUD/FORM plus terbutaline (n=441); BUD/FORM plus FORM (n=115); or salmeterol/fluticasone plus terbutaline (n=372). Demographic and baseline characteristics of the adolescent population are presented in table 2 (for demographics of the adult population (n=12 197), see online supplementary table S2). Within each study, baseline characteristics relating to disease history and severity were generally well balanced across treatment arms. Differences observed between studies in baseline parameters reflected differences in the mean asthma severity of patients recruited.

TABLE 2 Demographic and key baseline characteristics of the adolescent population

	Rabe [10]	Scicchitano [11]	O'Byrne [12]	Rabe [13]	Kuna [14]	Bousquet [15]	Overall[#]
Subjects	109	121	316	354	623	324	1847
Sex							
Male	55 (50.5)	71 (58.7)	185 (58.5)	225 (63.6)	399 (64.0)	202 (62.3)	1137
Female	54 (49.5)	50 (41.3)	131 (41.5)	129 (36.4)	224 (36.0)	122 (37.7)	710
Age years	14 (11–17)	14 (11–17)	14 (12–17)	14 (12–17)	14 (11–17)	14 (12–17)	14 (11–17)
Time since asthma diagnosis years[¶]	9 (0–17)	8 (0–17)	8 (0–17)	7 (0–17)	7 (0–17)	9 (0–18)	8 (0–18)
Daily ICS dose at entry µg	340.8 (200–625)	589.7 (400–1500)	552.9 (250–1000)	641.9 (400–1600)	664.6 (500–1600)	687.3 (250–1125)	579.5 (200–1600)
Use of LABA at entry[+]	30 (27.5)	31 (25.6)	75 (23.7)	218 (61.6)	220 (35.3)	135 (41.7)	709 (38.4)
Prebronchodilator FEV_1 % predicted	78.0 (56–109)	69.3 (44–93)	73.2 (52–90)	75.4 (50–99)	77.5 (30–132)	75.4 (50–132)	75.5 (30–132)
Reversibility %	20.4 (4–54)	26.5 (12–73)	20.5 (2–69)	23.9 (11–96)	24.4 (8–99)	24.9 (12–95)	23.6 (2–99)
Morning PEF $L \cdot min^{-1}$	330.8 (169–619)	345.7 (168–541)	343.6 (168–624)	367.2 (167–617)	360.6 (166–643)	346.6 (165–579)	353.8 (165–643)
Daily as-needed inhalations	1.41 (0.0–5.6)	1.62 (0.0–7.2)	2.28 (0.0–7.1)	1.45 (0.2–6.5)	1.96 (0.3–7.5)	2.22 (0.0–7.4)	1.91 (0.0–7.5)
Total symptom score (0–6)	1.04 (0.0–4.4)	1.73 (0.2–4.3)	1.17 (0.0–6.0)	1.65 (0.0–4.7)	1.85 (0.0–5.4)	2.05 (0.0–6.0)	1.67 (0.0–6.0)
Night-time awakenings %	10.0 (0–100)	15.9 (0–100)	13.0 (0–100)	23.2 (0–100)	28.2 (0–100)	29.3 (0–100)	22.9 (0–100)
ACQ-5	NC	NC	NC	1.862 (0.00–4.80)	1.824 (0.00–5.60)	1.764 (0.00–4.80)	1.818 (0.0–5.6)

Data are presented as n, n (%) or mean (range), unless otherwise stated. ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; ACQ-5: five-item asthma control questionnaire. [#]: in the budesonide/formoterol maintenance and reliever therapy arm, two patients received no treatment or there was no data on treatment; [¶]: data are presented as median (range); [+]: monoproduct or combination with ICS.

Efficacy

Primary end-point

For the primary end-point of time to first severe exacerbation, BUD/FORM MART was similar to or more effective than comparators in the adolescent population (figure 1) [10–15]. Hazard ratios (HRs) numerically favoured BUD/FORM MART for all treatment comparisons in five of the six studies (ranging from 0.15 to 0.93) [10–12, 14, 15], and were similar for BUD/FORM MART and comparator (BUD/FORM + FORM as needed) in the remaining study (HR 1.01) [13].

In the pooled analysis, the risk of a severe exacerbation was found to be lower with BUD/FORM MART than comparator in the adolescent population (HR 0.49, 95% CI 0.34–0.70) (figure 1). However, there was statistically significant heterogeneity in the pooled estimate (likelihood ratio test, p=0.04) (figure 1).

For time to first severe exacerbation, the results observed for the adolescent population, both in the individual studies and in the pooled analysis, were consistent with those observed for the adult population.

Secondary end-points

Forest plots for the secondary end-points of total number of severe exacerbations, asthma symptom scores, night-time awakenings, as-needed inhalations, FEV_1, morning PEF and ACQ-5 score are presented in figures 2, 3, 4 and 5. Box plots for as-needed inhalations are presented in figure 6. In the adolescent subgroup, point estimates were in favour of BUD/FORM MART for all secondary end-points in five of the six studies *versus* comparators [10–13, 15]. In addition, pooled estimates were in favour of BUD/FORM MART for these secondary end-points, although many of these analyses exhibited statistically significant heterogeneity (figures 2–5). For these secondary efficacy end-points, the results observed for the adolescent population, both in the individual studies and in the pooled analysis, were consistent with those observed for the adult population.

Fewer adolescent patients receiving BUD/FORM MART required OCS to manage severe exacerbations than those receiving comparators, although numbers were small (online supplementary table S3). Among adolescents, mean as-needed inhalation use was generally lower with BUD/FORM MART than comparators (figures 3c and 5), and mean as-needed use of BUD/FORM MART was consistently lower than adults across studies (range of means 0.43–0.85 *versus* 0.91–1.15 inhalations per day; figure 5). Among adolescents, use of >12 total inhalations of BUD/FORM on ⩾1 day was low (range 0.9–7.3%), and only one patient did so for >10 days (14 days).

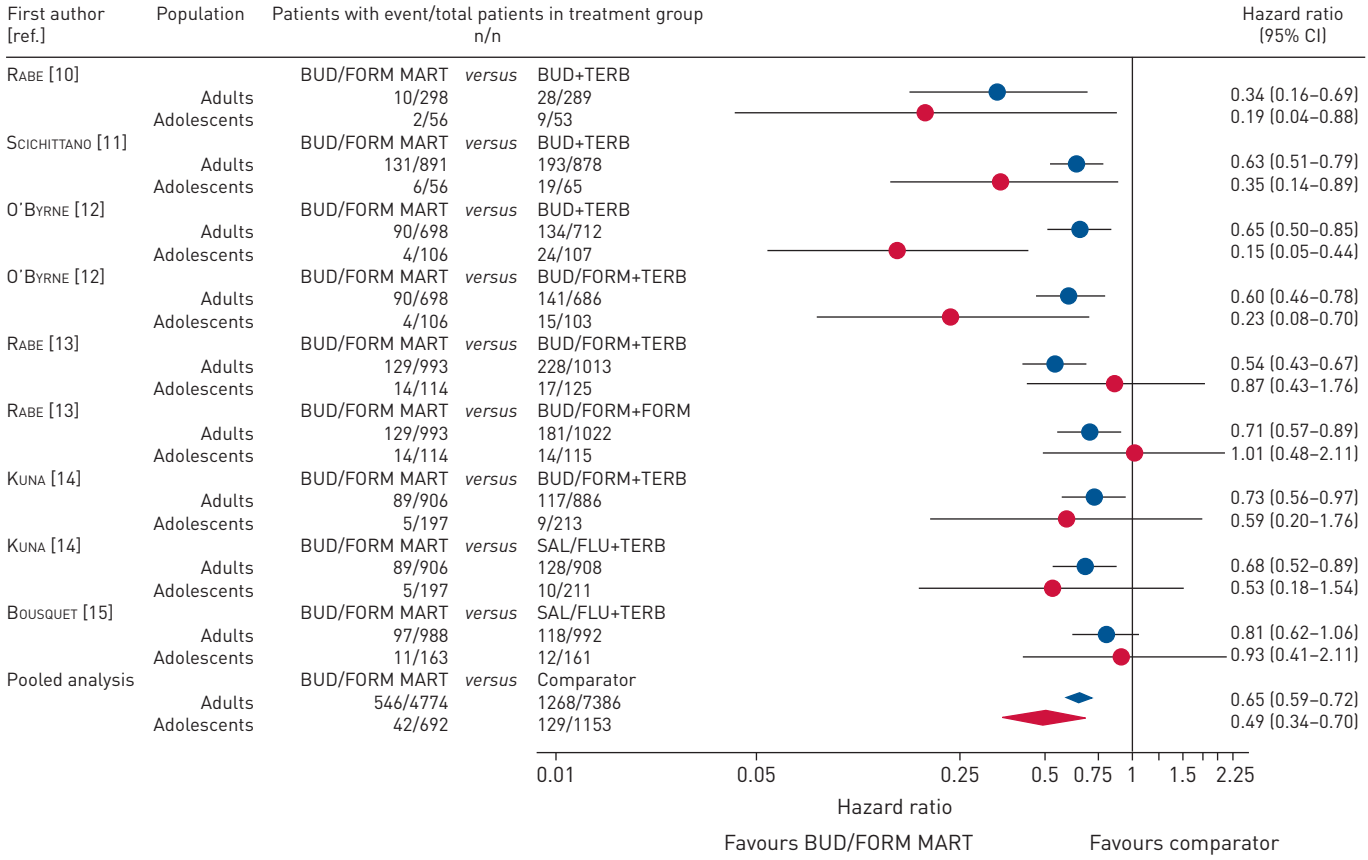


FIGURE 1 Forest plot of treatment comparisons for time to first severe exacerbation. Doses differ across studies (table 1). Estimates obtained from Cox regression models with treatment as a factor. Pooled analysis: Cox model stratified by study, budesonide/formoterol (BUD/FORM) *versus* not-BUD/FORM as a treatment variable and with country as a covariate. Heterogeneity p-values 0.1995 (adults) and 0.0435 (adolescents). MART: maintenance and reliever therapy; TERB: terbutaline; SAL/FLU: salmeterol/fluticasone.

ICS use

The BUD/FORM MART arms received a lower mean daily ICS dose than the comparator arms in four studies (online supplementary table S4 and figure S1) [10, 11, 14, 15]. The higher ICS daily dose for BUD/FORM MART *versus* BUD/FORM plus terbutaline as needed in the SD-039-0673 study [12] and both comparator arms in the SD-039-0734 study [13] was as expected based on the study design.

Safety

The incidence of adverse events and the types of adverse events reported were similar for adolescents receiving BUD/FORM MART and those receiving comparator treatments (online supplementary tables S5 and S6). The proportion of adolescents experiencing a serious adverse event or discontinuing due to an adverse event was very low and similar between treatment comparisons (online supplementary tables S5 and S6).

All treatments were well tolerated and there were no adverse events with fatal outcomes reported among adolescents using BUD/FORM MART or comparators.

Discussion

Despite the availability of effective treatments, asthma patients, regardless of age, continue to suffer from periodic worsening, which can further deteriorate to severe exacerbations in which medical intervention is required. Asthma is one of the most common chronic diseases in children and adolescents, but because it is highly variable during these periods of a patient's life, it is particularly difficult to manage, and morbidity among children and adolescents with asthma remains unacceptably high [20]. This analysis evaluates the totality of evidence from double-blind randomised controlled trials on the clinical efficacy and safety of BUD/FORM MART in adolescents with persistent asthma, an age group seldom studied. In six double-blind studies that included a total of 1847 adolescents [10–15], we found BUD/FORM MART

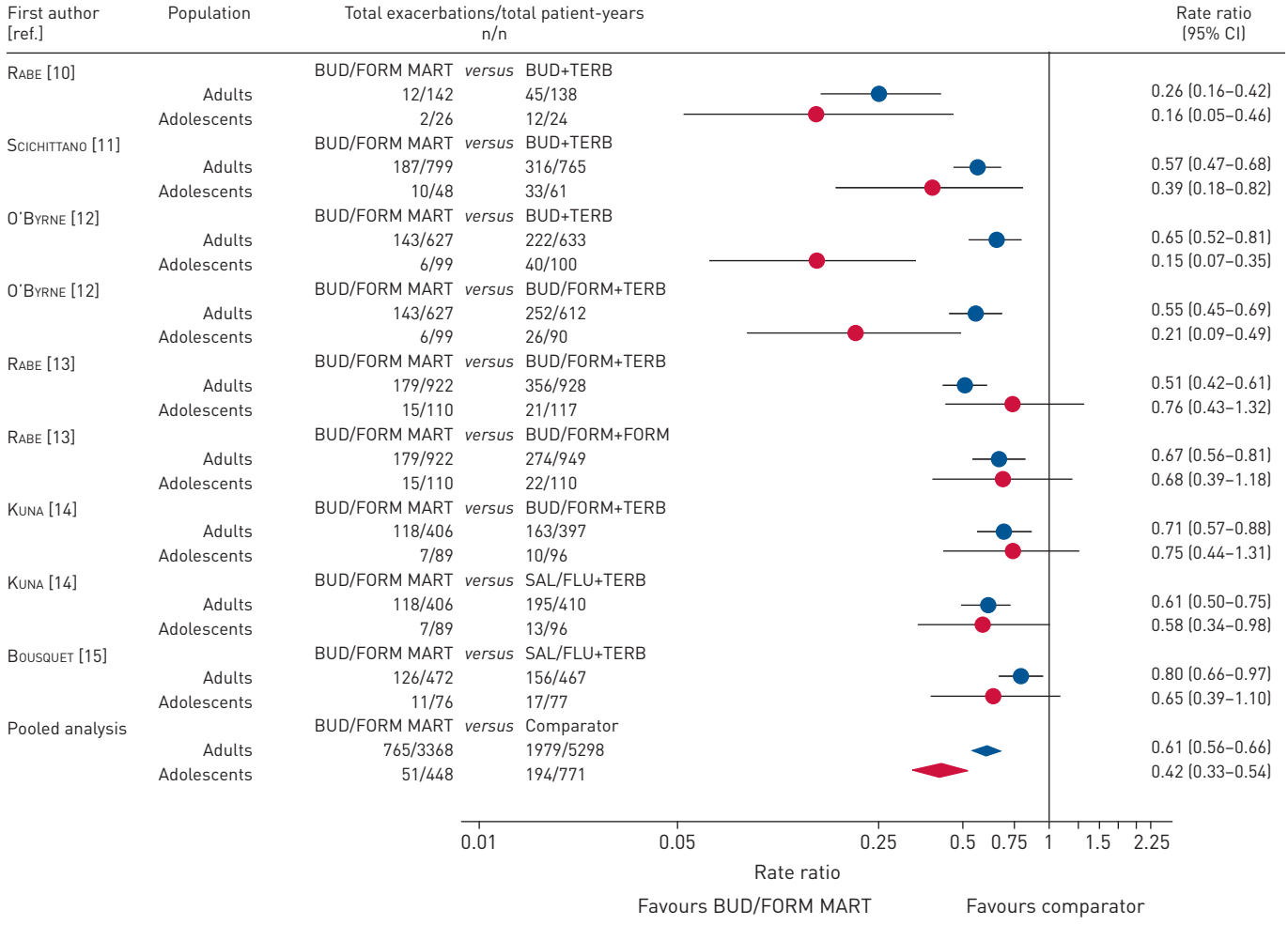
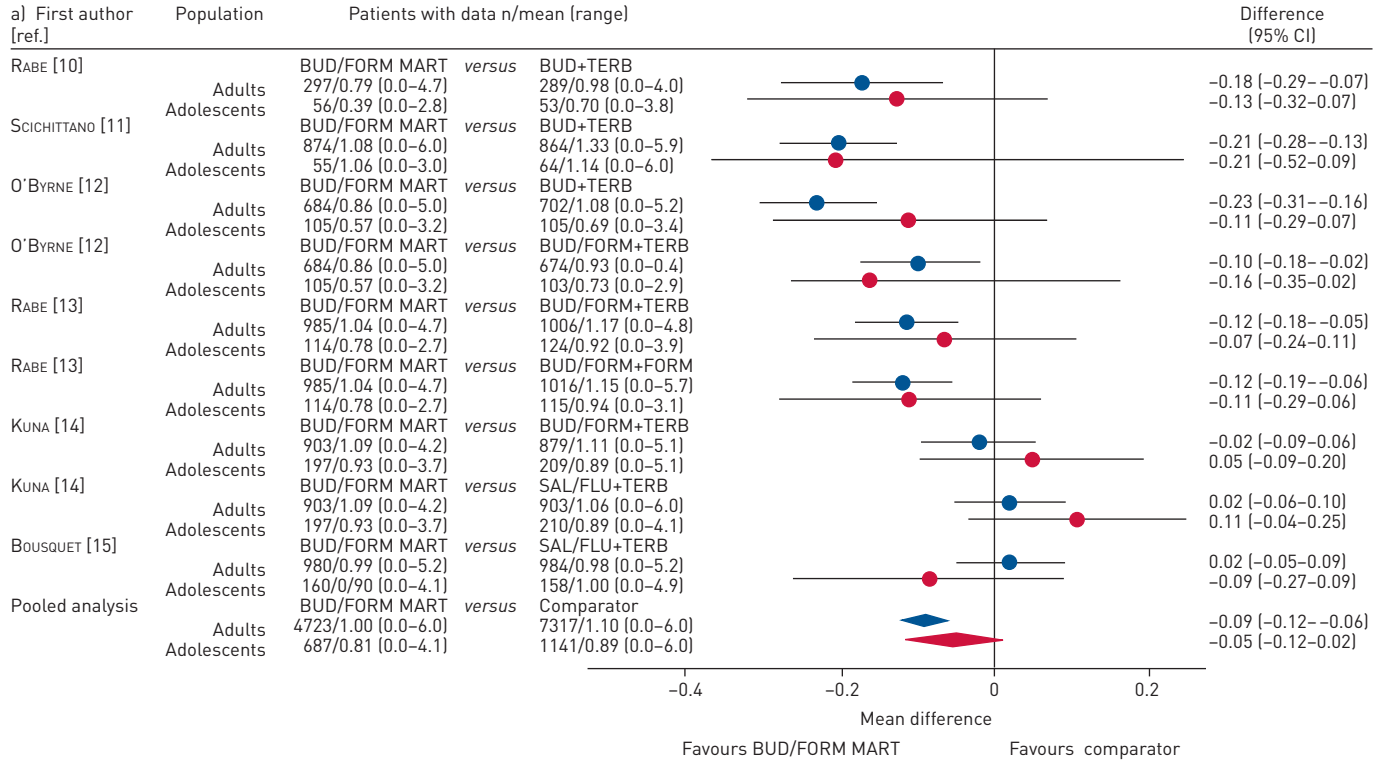


FIGURE 2 Forest plot of severe exacerbations (secondary end-point). Doses differ across studies (table 1). Estimates obtained from Poisson regression models with treatment as a factor, log time as an offset variable and adjusted for overdispersion. Pooled analysis: Poisson regression model with budesonide/formoterol (BUD/FORM) *versus* not-BUD/FORM as a treatment variable and with study as a covariate, log time as an offset and adjusted for overdispersion. Heterogeneity p-values 0.012 (adults) and 0.0262 (adolescents).

to be more efficacious than fixed high-dose ICS regimens (BUD), and comparable to or more efficacious than ICS/LABA comparator maintenance regimens (BUD/FORM and salmeterol/fluticasone) across a range of both clinically observed and patient-reported outcomes. The efficacy and safety profile observed in adolescents was generally consistent with that seen in adults. This consistency was evident both within and across clinical studies, and was independent of the comparator treatments selected and the maintenance dose of BUD/FORM used.

In the adolescent population in this analysis, point estimates favoured BUD/FORM MART in all six double-blind studies for number of severe exacerbations, and in five of these for the primary end-point of time to first severe exacerbation. The results for the secondary end-points support those of the primary end-point. These results were achieved despite the fact that adolescents randomised to BUD/FORM MART used a lower as-needed dose, and received a lower mean daily dose of ICS than those on comparator treatments in all studies where the clinical trial design allowed this comparison to be made. As concerns have previously been raised as to whether adolescents may overuse BUD/FORM MART (given that overuse of SABA is high in this age group), the finding that as-needed use in this patient group is lower than that observed with adults is encouraging.

The safety profile of BUD/FORM MART observed in the adolescent subgroups in the present analysis was in line with that reported previously in the literature for this regimen [10–15]. BUD/FORM MART was well tolerated by adolescent patients, and the frequency of ICS-related adverse events was very low, even in those with high as-needed use (online supplementary table S6). No deaths were reported, and no increased risk of systemic adverse events or new safety concerns was identified in the adolescent population.



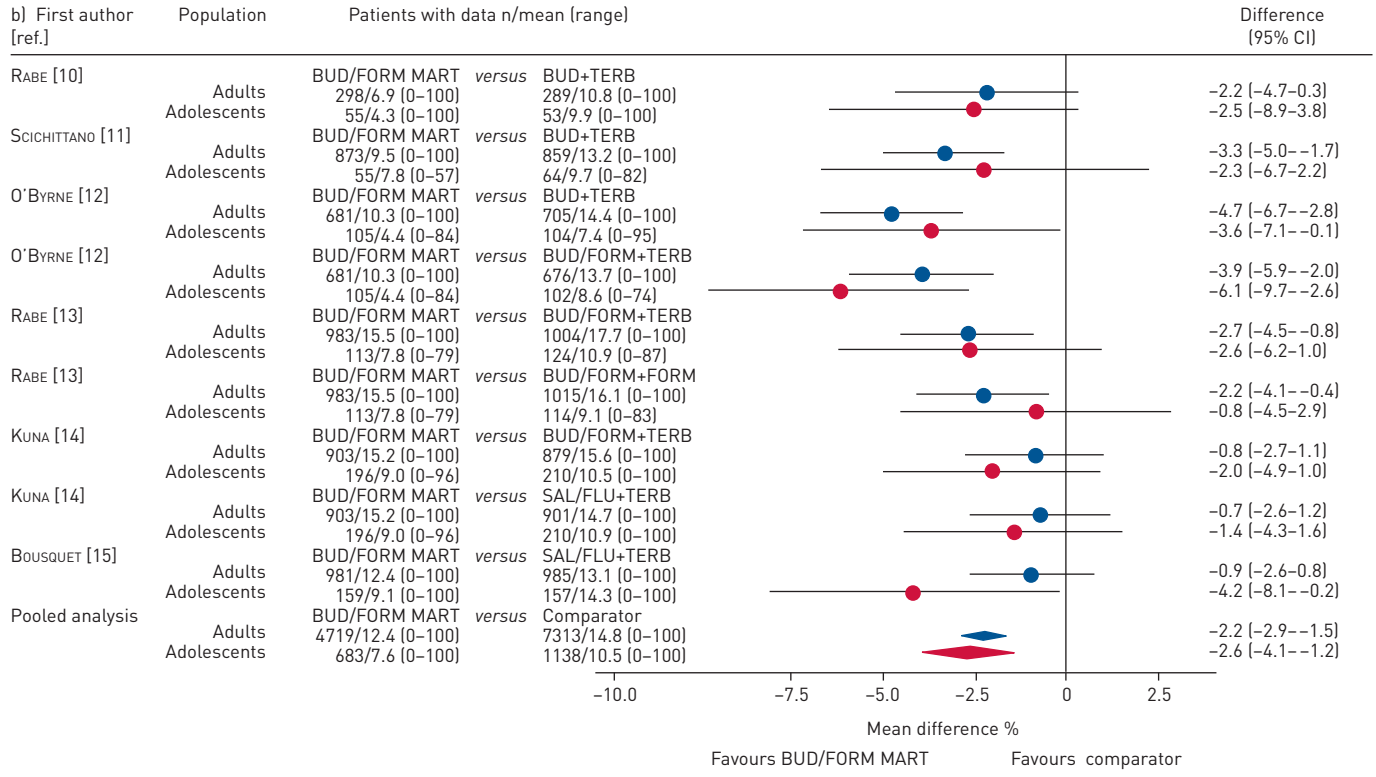
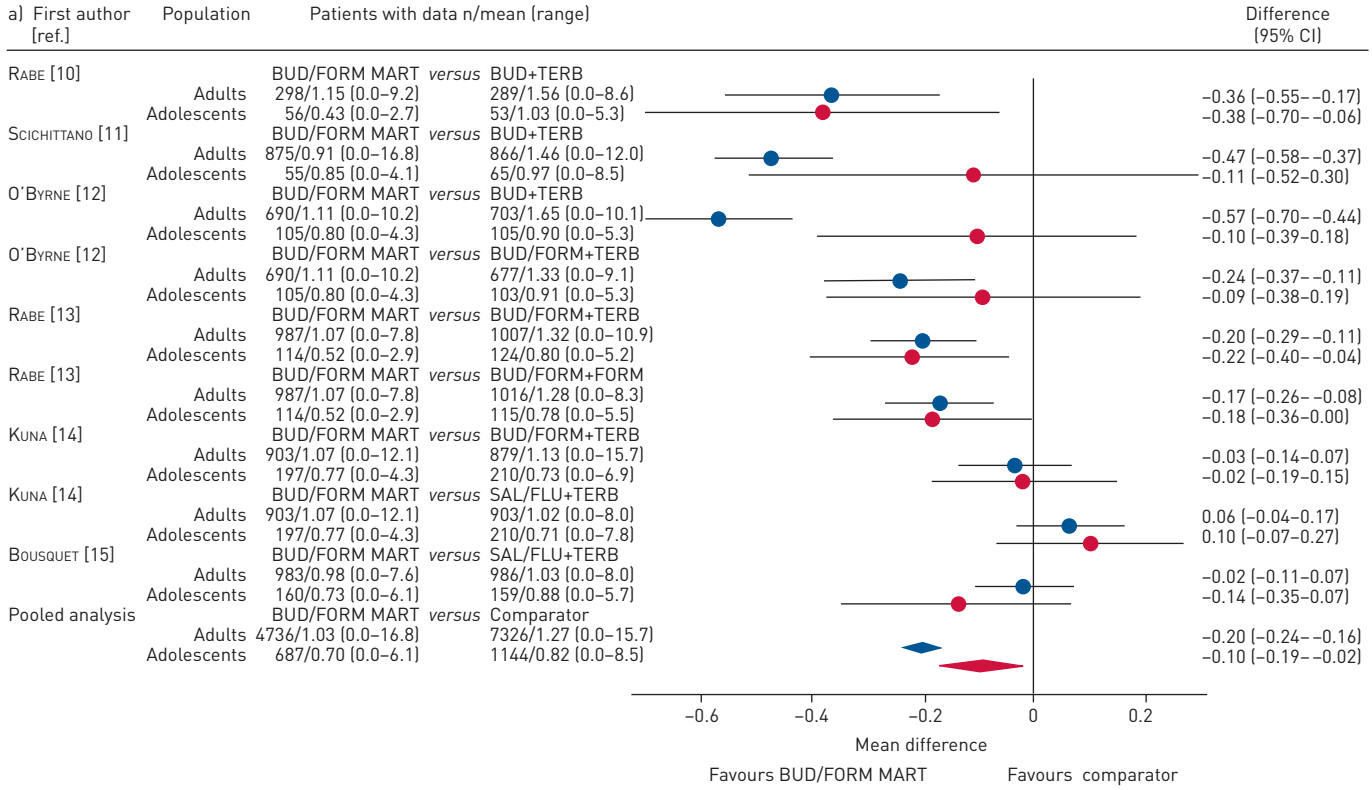


FIGURE 3 Forest plots of secondary end-points a) asthma symptom scores; b) night-time awakenings. Doses differ across studies (table 1). Estimates obtained using ANCOVA with change between run-in period mean and treatment period mean as the outcome variable, treatment as a factor and adjusting for the run-in period mean. Pooled analysis: ANCOVA model with budesonide/formoterol (BUD/FORM) *versus* not-BUD/FORM as a treatment variable, adjusting for run-in period mean and with study and country as covariates. Heterogeneity p-values a) <0.0001 (adults) and 0.2172 (adolescents); b) 0.038 (adults) and 0.5193 (adolescents). MART: maintenance and reliever therapy; TERB: terbutaline; SAL/FLU: salmeterol/fluticasone.



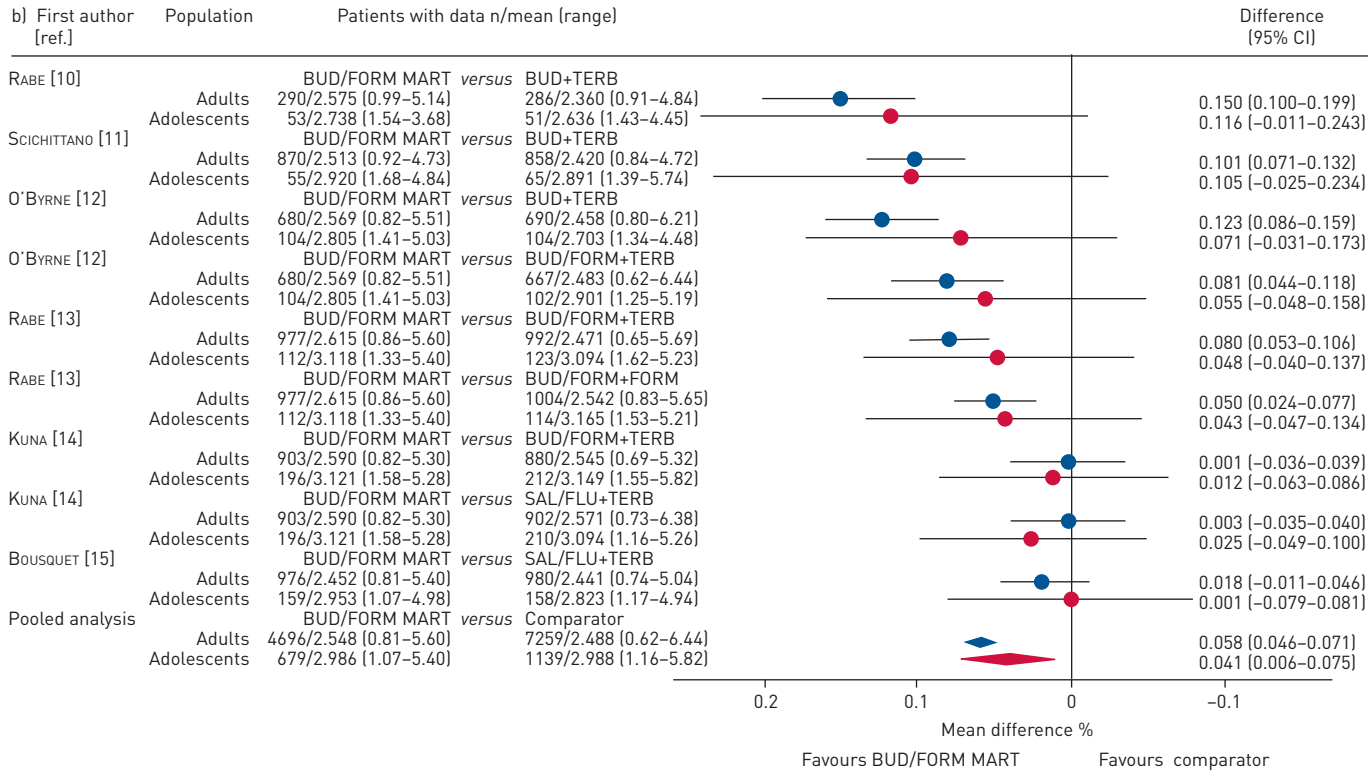


FIGURE 4 Forest plots of secondary end-points a) as-needed inhalations; b) forced expiratory volume in 1 s. Doses differ across studies (table 1). Estimates obtained using ANCOVA with change between run-in period mean and treatment period mean as the outcome variable, treatment as a factor and adjusting for the run-in period mean. Pooled analysis: ANCOVA model with budesonide/formoterol (BUD/FORM) *versus* not-BUD/FORM as a treatment variable, adjusting for run-in period mean, and with study and country as covariates. Heterogeneity p-values a) <0.0001 (adults) and 0.1311 (adolescents); b) <0.0001 (adults) and 0.6051 (adolescents). MART: maintenance and reliever therapy; TERB: terbutaline; SAL/FLU: salmeterol/fluticasone.

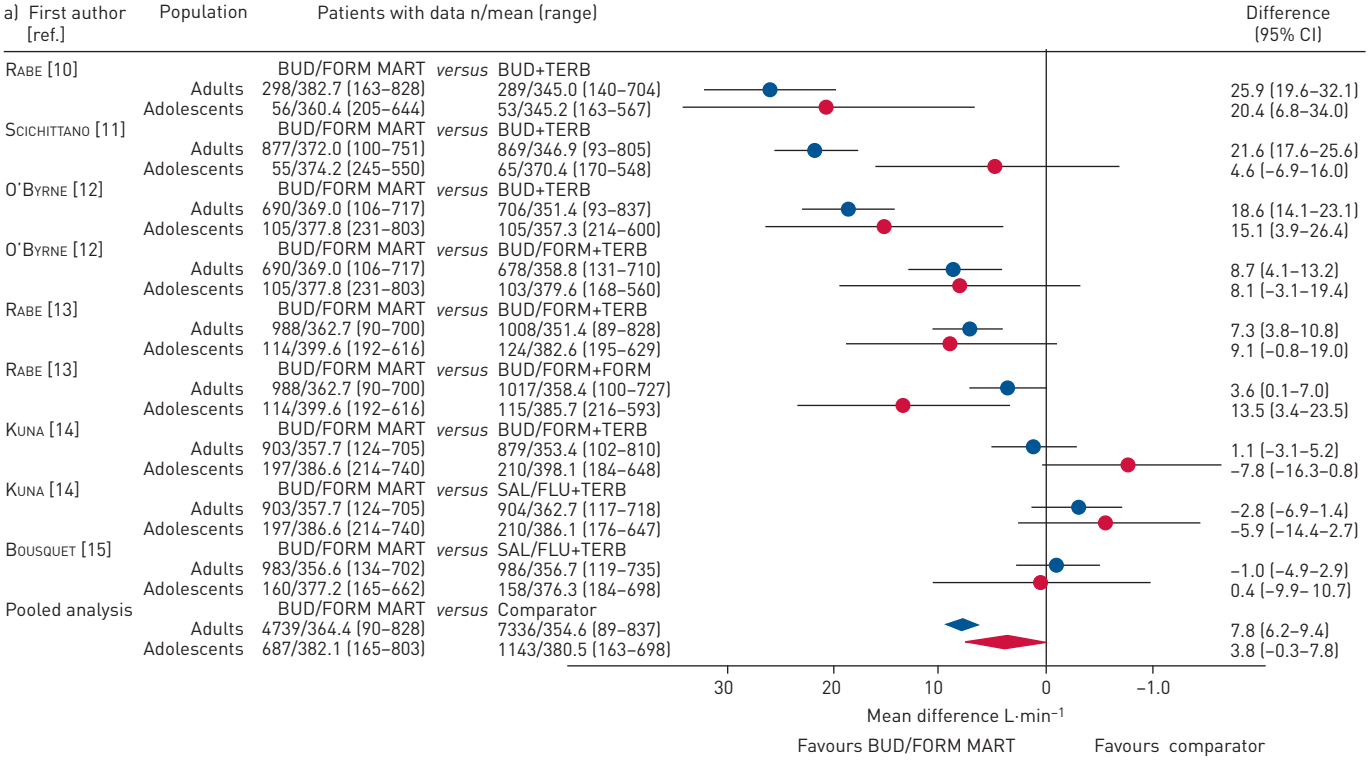


FIGURE 5 Forest plots of secondary end-points a) morning peak expiratory flow; b) 5-item asthma control questionnaire score. Doses differ across studies (table 1). Estimates obtained using ANCOVA with change between run-in period mean and treatment period mean as the outcome variable, treatment as a factor and adjusting for the run-in period mean. Pooled analysis: ANCOVA model with budesonide/formoterol (BUD/FORM) *versus* not-BUD/FORM as a treatment variable, adjusting for a) run-in period mean and b) randomisation visit value and with study and country as covariates. Heterogeneity p-values a) <0.0001 (adults) and 0.0026 (adolescents); b) 0.003 (adults) and 0.2383 (adolescents). MART: maintenance and reliever therapy; TERB: terbutaline; SAL/FLU: salmeterol/fluticasone.

The as-needed use of BUD/FORM in response to worsening symptoms allows for management of the underlying airway inflammation to prevent or diminish exacerbations (acting as an "anti-inflammatory reliever"), and is an important element of the BUD/FORM MART concept. ICS are the mainstay of asthma management and have been shown to reduce the morbidity associated with the disease [5]. However, poor adherence to regular ICS treatment can be associated with uncontrolled asthma and increased risk of exacerbation [21, 22]. Adherence to regular asthma maintenance therapy often declines during adolescence [5, 23], as patients start to take more responsibility for their asthma care, and gain greater independence. It has been suggested that adherence in this population is partly dependent on the

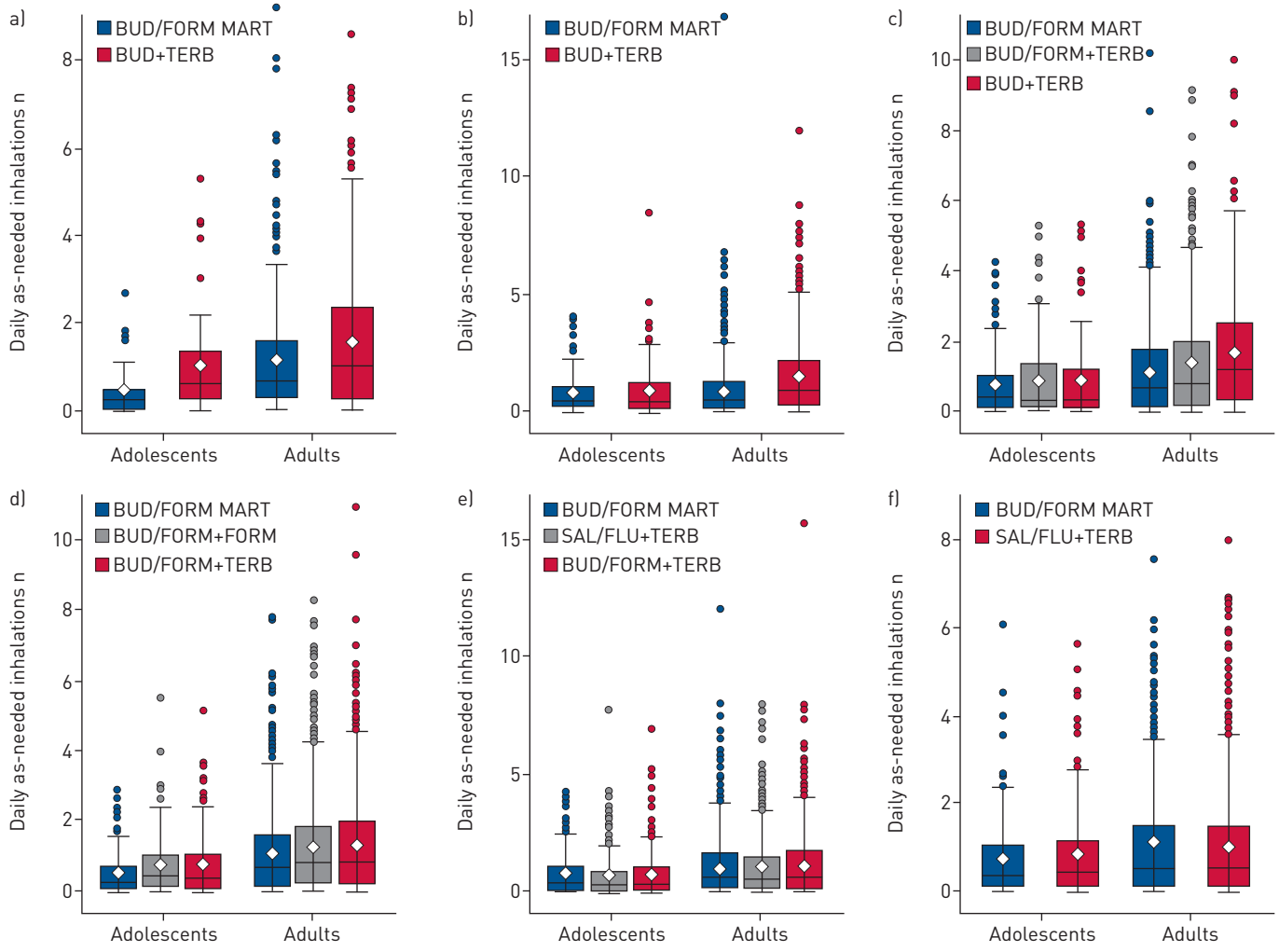


FIGURE 6 Box plots of mean numbers of as-needed inhalations in adolescents and adults. a) Rabe *et al.* [10]; b) Scichittano *et al.* [11]; c) O'Byrne *et al.* [12]; d) Rabe *et al.* [13]; e) Kuna *et al.* [14]; e) Bousquet *et al.* [15]. The mean is represented by a hollow diamond and the median as a horizontal line within each box. The bottom and top of the box represent the 25th and 75th percentiles, respectively. Outliers are represented by circles and are defined as those observations that lie beyond the upper quartile plus 1.5 times the interquartile range. The whiskers extend to the most extreme non-outlying value. BUD/FORM: budesonide/formoterol; MART: maintenance and reliever therapy; TERB: terbutaline; SAL/FLU: salmeterol/fluticasone.

overall balance of the perceived benefits of the medication and the perceived adverse events [4, 5, 8]. Consequently, treatment regimens should be tailored to the needs, lifestyle and psychosocial status of the adolescent with asthma [1]. Using a single BUD/FORM inhaler for both maintenance and relief may help to overcome poor adherence to regular maintenance therapy by ensuring that patients receive their ICS whenever they require an additional dose for symptom relief and experience rapid-onset bronchodilation due to FORM.

The data source for this analysis was the AstraZeneca clinical study database, allowing access to individual patient data. To check whether there were any additional non-AstraZeneca sponsored studies that could have been considered, we conducted a review of the literature, searching for randomised controlled trials evaluating a combination of ICS and any rapid-acting bronchodilator in a single inhaler for both maintenance and as-needed relief of symptoms in adolescents with persistent asthma. The literature search identified the six studies included in this analysis and found no additional studies meeting the inclusion criteria for this analysis; hence we believe that the present analysis reflects the totality of data at the time of writing.

This analysis is subject to several limitations. Despite a large overall "pool" of adolescents for evaluation, the number of adolescents in each study was relatively low, and hence the analyses were insufficiently powered to demonstrate evidence of a treatment effect in adolescents within each study. This is evident in the wide confidence intervals for the estimated treatment effects. While pooling data across the six studies

resulted in much tighter confidence intervals, the pooled estimates should be treated with caution given that the studies included had different designs, comparators and dosages, and many of the formal statistical tests of heterogeneity for the pooled estimates indicated that a single pooled estimate across studies for a subgroup was questionable. Evaluation of baseline disease characteristic data across the trials suggests that the level of asthma severity may have been slightly lower in the adolescent population than the adult population, and it is possible that this may have contributed in part towards the observation of lower BUD/FORM as-needed use in the adolescent subgroup. Another possible limitation is that the calculation of mean daily ICS dose was based on the prescribed maintenance dose, assuming full compliance (as well as on the number of as-needed inhalations recorded in e-diaries in the case of BUD/FORM MART).

The comparator regimens included in this analysis reflect asthma treatment guidelines at the time that each study was conducted (2001–2006); however, all remain treatment options for steps 3–5 of the current GINA guidelines, and therefore remain appropriate comparators [1].

The management of persistent asthma in adolescence is particularly challenging; adherence to regular maintenance therapy is typically poor, asthma control generally suboptimal, and morbidity unacceptably high. Previous randomised controlled trials that included patients aged ⩾12 years have shown that BUD/FORM given both as maintenance and reliever therapy significantly reduces the risk of severe exacerbations when compared with ICS/LABA maintenance (or high-dose ICS) plus SABA in patients with persistent asthma, while achieving at least similar levels of asthma control and at a lower long-term steroid load. This *post hoc* analysis demonstrates that the efficacy benefits (including reduction in severe exacerbations) and the safety of BUD/FORM MART in the adolescent subgroups of these trials are consistent with those reported for adults and for the overall study populations. These efficacy benefits in adolescents were achieved with lower mean as-needed medication use than comparators, and lower BUD/FORM as-needed use in adolescents than adults. These findings support the use of BUD/FORM MART in adolescents with persistent asthma, and are of particular clinical relevance given the challenges in treating this age group.

Acknowledgements

The manuscript was developed by the authors, with the assistance of a medical writer, funded by AstraZeneca. Medical writing assistance was provided by Claire Mwape and Katharine Williams (inScience Communications, Springer Healthcare, Chester, UK), in accordance with Good Publication Practice (GPP3) guidelines (www.ismpp.org/gpp3).

Author contributions: All authors contributed to data interpretation, and conceiving, writing and revising the manuscript. D. Lythgoe was responsible for statistical analyses. All authors had full access to all the data in the analysis and H. Bisgaard (the corresponding author) had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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