Supplementary materials

Methods

Definition and calculation of severe exacerbations

The first three studies conducted [10-12], defined severe exacerbations as the need for oral corticosteroid (OCS) and/or hospitalisation/emergency room care due to asthma and/or a decrease in peak expiratory flow (PEF) of ≥30% on two consecutive days compared with the run-in period. In these studies, exacerbations were to be treated with a 10-day OCS course; an exacerbation lasting >10 days was considered a new exacerbation on the 11th day. Based on this experience, the later three studies [13-15] did not include falls in PEF in the exacerbation definition, nor this stipulated OCS treatment time, defining a severe exacerbation as the need for OCS for ≥3 days and/or hospitalisation/emergency room care due to asthma worsening.

For the purpose of this analysis, we defined a severe exacerbation as the need for OCS (for ≥3 days [10-12]) and/or hospitalisation/emergency room care due to asthma worsening; to align with this definition, data from 3 of the included studies [13-15] were reanalysed to exclude PEF fall from the exacerbation definition.

Literature review to identify any additional studies

We conducted a review to identify any additional randomised controlled trials (RCTs) evaluating a combination of inhaled corticosteroids (ICS) and a rapid-acting bronchodilator in a single inhaler for both maintenance and as-needed relief of symptoms in adolescents with persistent asthma. We searched PubMed using the following string:

((Asthma[MeSH Terms] AND (adolescent [MESH Terms]) AND (*corticosteroid OR corticosteroid* OR budesonide OR fluticasone OR beclometasone OR beclomethasone OR mometasone OR ciclesonide) AND (formoterol OR short-acting beta2 agonist* OR short-acting beta2-agonist* OR SABA OR salbutamol OR albuterol OR levosalbutamol OR metaproterenol OR levalbuterol OR pirbuterol) AND (maintenance) AND (rescue OR relief OR reliever OR 'as needed' OR 'as required' OR 'as-needed' OR 'as-required' OR prn) AND randomized controlled trial[Publication Type] AND (("2000/01/01"[EDAT] to "2016/01/01"[EDAT]) OR ("2000/01/01"[PDAT]: "2016/01/01"[PDAT])). This search was also run across the Cochrane Database, but did not yield any relevant results.

Initially, 52 titles were identified, reduced to 22 after review of titles and abstracts. An additional 10 publications were excluded on further evaluation of the full paper as they were either *post-hoc* analyses of already included studies (n=6) or they did not include patients <18 years (n=5). A total of 12 studies (6 double-blind and 6 open-label) that evaluated an ICS/rapid-acting bronchodilator as maintenance and reliever therapy (MART) and that included adolescents in the study population remained for evaluation; all of these evaluated budesonide/formoterol (BUD/FORM) (citation details below). Of these, 6 were open-label studies and therefore not eligible for inclusion in the analysis. The 6 double-blind studies remaining are the same 6 studies included in the analysis presented in this paper.

Double-blind studies	**Open-label studies**
Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007; 101(12): 2437–46.	Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. Int J Clin Pract. 2009; 63(10): 1479–88.
Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007; 61(5): 725–36.*	Lundborg M, Wille S, Bjermer L, Tilling B, Lundgren M, Telg G, et al. Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. Curr Med Res Opin. 2006; 22(5): 809–21.
O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171(2): 129–36.	Sears MR, Boulet LP, Laviolette M, Fitzgerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. The European respiratory journal. 2008; 31(5): 982–9.
Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006; 129(2): 246–56.	Soes-Petersen U, Kava T, Dahle R, Lei Y, Dam N. Budesonide/formoterol maintenance and reliever therapy versus conventional best standard treatment in asthma in an attempted 'real life' setting. Clin Respir J. 2011; 5(3): 173–82.
Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006; 368(9537): 744–53.	Stallberg B, Ekstrom T, Neij F, Olsson P, Skoogh BE, Wennergren G, et al. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respir Med. 2008; 102(10): 1360–70.
Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004; 20(9): 1403–18.	Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? The European Respiratory Journal. 2005; 26(5): 819–28.

*Only study to report data separately for the adolescent population

Supplementary appendix

Table S1: Key entry criteria

	Rabe et al, 2006a (SD-039-0667) [10]	Scicchitano et al, 2004 (SD-039-0668) [11]	O'Byrne et al, 2005 (SD-039-0673) [12]	Rabe et al, 2006b (SD-039-0734) [13]	Kuna et al, 2007 (SD-039-0735) [14]	Bousquet et al, 2007 (NCT00242775) [15]
Inclusion criteria						
Daily ICS dose (μg)	200–500	400–1600	400–1000 (200–500 for ages 4–11)	400–1600 with LABA 800–1600 without LABA	≥500 fluticasone/ budesonide or ≥1000 other GCS	400–1000 with LABA 800–1600 without LABA
FEV_1 (% PN)	60–100	50–90	60–90 (60–100 for ages 4–11)	50–100	≥50	≥50
Other	NS	≥1 asthma exacerbation 1–12 months prior to visit 1	≥1 asthma exacerbation 1–12 months prior to visit 1	≥1 asthma exacerbation 1–12 months prior to visit 1	≥1 asthma exacerbation 1–12 months prior to visit 1	≥1 asthma exacerbation 1–12 months prior to visit 1
Randomisation criteria						
As-needed inhalations during run-in	Total ≥7 on last 10 days	NS	Total ≥12 (≥8 for ages 4–11) on last 10 days	Use on at least 5 of last 7 days	Use on at least 5 of last 7 days	Use on at least 5 of last 7 days
Symptom score during run-in (on a scale of 0–6)	NS	≥1 on at least 4 of last 7 days	NS	NS	NS	NS

FEV_1 (% P.N.): forced expiratory volume in one second as a percentage of predicted normal; ICS: inhaled glucocorticosteroid; LABA long-acting β_2-agonist; NS not specified; PN predicted normal.

Table S2: Demographic and key baseline characteristics of the adult population

	Rabe et al, 2006a (SD-039-0667) [10]	Scicchitano et al, 2004 (SD-039-0668) [11]	O'Byrne et al, 2005 (SD-039-0673) [12]	Rabe et al, 2006b (SD-039-0734) [13]	Kuna et al, 2007 (SD-039-0735) [14]	Bousquet et al, 2007 (NCT00242775) [15]	Overall
	N=588	N=1769	N=2103	N=3040	N=2712	N=1985	N=12197
Sex, n (%)							
Male	215 (36·6)	727 (41·1)	809 (38·5)	1120 (36·8)	1012 (37·3)	685 (34·5)	4568 (37·5)
Female	373 (63·4)	1042 (58·9)	1294 (61·5)	1920 (63·2)	1700 (62·7)	1300 (65·5)	7629 (62·5)
Age (years), mean (range)	42 (18-79)	45 (18-80)	43 (18-79)	45 (18-89)	43 (18-83)	44 (18-80)	44 (18-89)
Time since asthma diagnosis (years), median (range)	10 (0-69)	13 (0-71)	11 (0-68)	10 (0-76)	10 (0-69)	16 (0-77)	11 (0-77)
Daily ICS dose at entry (µg), mean (range)	351·9 (200-625)	757·1 (250-2000)	670·6 (250-1200)	770·0 (200-1600)	766·2 (100-3200)	733·9 (200-2000)	675·0 (100-3200)
Use of LABA at entry* n (%)	107 (18·2)	789 (44·6)	629 (29·9)	1773 (58·3)	1311 (48·3)	1132 (57·0)	5741 (47·1)
Prebronchodilator FEV_1 (% PN), mean (range)	74·6 (51-123)	70·2 (37-102)	72·9 (43-108)	71·4 (30-115)	71·5 (29-143)	69·8 (45-222)	71·4 (29-222)
Reversibility (%), mean (range)	19·1 (-3-101)	23·5 (7-171)	20·9 (3-79)	23·7 (0-132)	23·8 (3-150)	23·7 (7-103)	23.0 (-3-171)
Morning PEF (L/min), mean (range)	341·4 (127-734)	336·7 (77-749)	338·3 (69-725)	345·1 (93-721)	330·6 (95-885)	326·7 (107-730)	336·3 (69-885)
Daily as-needed inhalations, mean (range)	1·76 (0·0-8·2)	1·95 (0·0-15·6)	2·57 (0·0-13·5)	1·94 (0·0-9·7)	2·40 (0·0-12·4)	2·27 (0·0-8·4)	2·20 (0·0-15·6)
Total symptom score (0–6), mean (range)	1·33 (0·0-4·7)	1·88 (0·0-6·0)	1·57 (0·0-5·6)	1·73 (0·0-6·0)	1·95 (0·0-6·0)	1·86 (0·0-6·0)	1·78 (0·0-6·0)
Night-time awakenings (%), mean (range)	17·0 (0-100)	23·5 (0-100)	23·7 (0-100)	31·1 (0-100)	34·3 (0-100)	32·6 (0-100)	29·0 (0-100)
ACQ-5, mean (range)	NC	NC	NC	1·909 (0·00-5·40)	2·020 (0·00-5·20)	1·877 (0·00-5·40)	1·940 (0·00-5·4)

*Monoproduct or combination with ICS.

ACQ-5, 5-item asthma control questionnaire; FEV_1 (% PN), forced expiratory volume in 1 second as a percentage of predicted normal; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; NC, not collected; PEF, peak expiratory flow.

Table S3: Number (%) of patients taking oral corticosteroids for severe exacerbations: BUD/FORM MART versus comparators*

Study**	BUD/FORM MART	BUD + TERB	BUD/FORM + TERB	BUD/FORM + FORM	SAL/FLU + TERB
Rabe et al, 2006a† (SD-039-0667) [10]	3 (5·4)	10 (18·9)	-	-	-
Scicchitano et al, 2004† (SD-039-0668) [11]	6 (10·7)	19 (29·2)	-	-	-
O'Byrne et al, 2005 (SD-039-0673) [12]‡	5 (4·7)	25 (23·4)	15 (14·6)	-	-
Rabe et al, 2006 (SD-039-0734) [13]	12 (10·5)	-	13 (10·4)	13 (11·3)	-
Kuna et al, 2007 (SD-039-0735) [14]†	5 (2·5)	-	7 (3·3)	-	8 (3·8)
Bousquet et al, 2007 (NCT00242775) [15]	10 (6·1)	-	-	-	11 (6·8)

BUD, budesonide; FLU, fluticasone; FORM, formoterol; MART, maintenance and reliever therapy; SAL, salmeterol; TERB, terbutaline.

*Falls in PEF of ≥30% are included for Rabe et al, 2006a, Scicchitano et al, 2004 and O'Byrne et al, 2005 [10-12].

**The treatment period duration was 6 months in Rabe et al, 2006a, Kuna et al, 2007 and Bousquet et al, 2007 [10, 14, 15] and 12 months in Scicchitano et al, 2004, O'Byrne et al, 2005 and Rabe et al, 2006b [11-13]. For 6-month studies, data are extrapolated to 1 year for cross-study comparison.

†One 11 year-old is included in the adolescent subgroup for Rabe et al, 2006a and Scicchitano et al, 2004 [10, 11] and two 11 year-olds are included in the adolescent subgroup for Kuna et al, 2007 [14].

‡Children were recruited in the O'Byrne et al, 2005 study [12], but were not included in the current analysis.

Table S4: Summary of ICS use

	BUD dose in BUD/FORM MART arms			Mean total daily ICS dose (µg) in comparator arms			
Study	**Maintenance dose (µg)**	**Mean as-needed inhalations per day**	**Mean total daily dose[†] (µg)**	**BUD + TERB [ICS: BUD]**	**BUD/FORM + TERB [ICS: BUD]**	**BUD/FORM + FORM [ICS: BUD]**	**SAL/FLU + TERB [ICS: FLU]**
Rabe et al, 2006a (SD-039-0667) [10]	160	0·43	192·9	320			
Scicchitano et al, 2004 (SD-039-0668) [11]	320	0·85	445·7	640			
O'Byrne et al, 2005 (SD-039-0673) [12]	160	0·80	220·1	640	160		
Rabe et al, 2006b (SD-039-0734) [13]	320	0·52	402·3		320	320	
Kuna et al, 2007 (SD-039-0735) [14]	320	0·77	441·3		640		500[‡]
Bousquet et al, 2007 (NCT00242775) [15]	640	0·73	746·9				1000[‡]

BUD, budesonide; FLU, fluticasone; FORM, formoterol; ICS: inhaled glucocorticosteroid; MART, maintenance and reliever therapy; SAL, salmeterol; TERB, terbutaline.
All budesonide doses expressed as delivered dose. For the non-BUD/FORM MART arms total daily dose is the maintenance dose.

[†]Assuming full compliance. For the BUD/FORM MART arm, the mean total daily dose cannot be calculated directly from the sum of the maintenance dose and the mean number of as-needed inhalations multiplied by the as-needed dose presented in this table because this will introduce non-negligible rounding errors. These rounding errors were avoided in the underlying calculations used to produce the mean total daily doses presented in this table.
[‡]Estimated equipotent dose for 500 µg of fluticasone is 800 µg budesonide in GINA 2010.

Table S5: BUD/FORM MART versus treatment comparison pools: number (%) of adolescents who had an AE in any category in studies (safety population)

Category of AEs* **Rabe et al, 2006a (SD-039-0667) [10], Scicchitano et al, 2004 (SD-039-0668) [11] and O'Byrne et al, 2005 (SD-039-0673) [12]**	**BUD/FORM MART (n=218)** **n (%)**	**BUD + TERB as needed (n=225)** **n (%)**
Any AEs	114 (52·3)	123 (54·7)
SAEs	8 (3·7)	14 (6·2)
SAEs leading to death	0	0
Discontinuation due to AEs	2 (0·9)	2 (0·9)
O'Byrne et al, 2005 (SD-039-0673) [12], Rabe et al, 2006b (SD-039-0734) [13] and Kuna et al, 2007 (SD-039-0735) [14]	**BUD/FORM MART (n=417)** **n (%)**	**BUD/FORM + TERB as needed (n=441)** **n (%)**
Any AEs	195 (46·8)	180 (40·8)
SAEs	10 (2·4)	13 (2·9)
SAEs leading to death	0	0
Discontinuation due to AEs	4 (1·0)	3 (0·7)
Kuna et al, 2007 (SD-039-0735) [14] and Bousquet et al, 2007 (NCT00242775) [15]	**BUD/FORM MART (n=360)** **n (%)**	**SAL/FLU + TERB as needed (n=372)** **n (%)**
Any AEs	119 (33·1)	117 (31·5)
SAEs	3 (0·8)	5 (1·3)
SAEs leading to death	0	0

Discontinuation due to AEs	5 (1.4)	1 (0.3)

Bousquet et al, 2007 (NCT00242775) [15]	**BUD/FORM MART (n=163) n (%)**	**SAL/FLU + TERB as needed (n=161) n (%)**
Any AEs	49 (30·1)	55 (34·2)
SAEs	1 (0·6)	4 (2·5)
SAEs leading to death	0	0
Discontinuation due to AEs	2 (1·2)	1 (0·6)

AE, adverse event; BUD, budesonide; FLU, fluticasone; FORM, formoterol; MART, maintenance and reliever therapy; n, number of patients; SAE, serious adverse event; SAL, salmeterol; TERB, terbutaline

*Includes patients with AEs ongoing during randomised treatment and the corresponding follow-up period, if applicable. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

Table S6: Number (%) adolescents with the most common AEs (frequency of >3% in any treatment group) presented by the preferred term.

Preferred term*,** **Rabe et al, 2006a (SD-039-0667) [10], Scicchitano et al, 2004 (SD-039-0668) [11] and O'Byrne et al, 2005 (SD-039-0673) [12]**	**BUD/FORM MART (n=218)** **n (%)**	**BUD + TERB as-needed (n=225)** **n (%)**
Nasopharyngitis	22 (10·1)	17 (7·6)
Upper respiratory tract infection	13 (6·0)	21 (9·4)
Bronchitis	5 (2·3)	9 (4·0)
Headache	13 (6·0)	19 (8·5)
Rhinitis	14 (6·4)	16 (7·2)
Sinusitis	7 (3·2)	12 (5·4)
Pharyngitis	15 (6·9)	23 (9·9)
Asthma	3 (1·4)	13 (5·8)
Respiratory tract infection	7 (3·2)	9 (4·0)
Influenza	6 (2·8)	10 (4·5)
Oropharyngeal pain	8 (3·7)	5 (2·2)
Tonsillitis	8 (3·7)	5 (2·2)
O'Byrne et al, 2005 (SD-039-0673) [12], Rabe et al, 2006b (SD-039-0734) [13] and Kuna et al, 2007 (SD-039-0735) [14]	**BUD/FORM MART (n=417)** **n (%)**	**BUD/FORM + TERB as-needed (n=441)** **n (%)**
Nasopharyngitis	36 (8·6)	36 (8·2)
Upper respiratory tract infection	23 (5·5)	13 (2·9)
Bronchitis	14 (3·4)	15 (3·4)
Pharyngitis	26 (6·2)	25 (5·7)
Rhinitis	19 (4·6)	20 (4·5)
Influenza	16 (3·8)	11 (2·5)
Headache	9 (2·2)	13 (2·9)
Sinusitis	14 (3·4)	11 (2·5)
Asthma	4 (1·0)	8 (1·8)
Tonsillitis	13 (3·1)	10 (2·3)
Kuna et al, 2007 (SD-039-0735) [14] and Bousquet et al, 2007 (NCT00242775) [15]	**BUD/FORM MART (n=360)** **n (%)**	**SAL/FLU + TERB as-needed (n=372)** **n (%)**
Upper respiratory tract infection	15 (4·2)	14 (3·8)
Nasopharyngitis	18 (5·0)	17 (4·6)
Bronchitis	10 (2·8)	9 (2·4)
Pharyngitis	18 (5·0)	22 (5·9)

Preferred term*/**		
Rabe et al, 2006a (SD-039-0667) [10], Scicchitano et al, 2004 (SD-039-0668) [11] and O'Byrne et al, 2005 (SD-039-0673) [12]	**BUD/FORM MART (n=218) n (%)**	**BUD + TERB as-needed (n=225) n (%)**
Nasopharyngitis	22 (10·1)	17 (7·6)
Upper respiratory tract infection	13 (6·0)	21 (9·4)
Bronchitis	5 (2·3)	9 (4·0)
Headache	13 (6·0)	19 (8·5)
Rhinitis	14 (6·4)	16 (7·2)
Sinusitis	7 (3·2)	12 (5·4)
Pharyngitis	15 (6·9)	23 (9·9)
Asthma	3 (1·4)	13 (5·8)
Respiratory tract infection	7 (3·2)	9 (4·0)
Influenza	6 (2·8)	10 (4·5)
Oropharyngeal pain	8 (3·7)	5 (2·2)
Tonsillitis	8 (3·7)	5 (2·2)
O'Byrne et al, 2005 (SD-039-0673) [12], Rabe et al, 2006b (SD-039-0734) [13] and Kuna et al, 2007 (SD-039-0735) [14]	**BUD/FORM MART (n=417) n (%)**	**BUD/FORM + TERB as-needed (n=441) n (%)**
Headache	4 (1·1)	4 (1·1)
Sinusitis	12 (3·4)	13 (3·5)
Influenza	11 (3·1)	9 (2·4)
Bousquet et al, 2007 (NCT00242775) [15]	**BUD/FORM MART (n=163) n (%)**	**SAL/FLU + TERB as-needed (n=161) n (%)**
Upper respiratory tract infection	8 (4·9)	9 (5·6)
Nasopharyngitis	13 (8·0)	10 (6·2)
Bronchitis	3 (1·8)	5 (3·1)
Headache	3 (1·8)	0
Pharyngitis	2 (1·2)	6 (3·7)
Sinusitis	3 (1·8)	4 (2·5)
Influenza	5 (3·1)	3 (1·9)

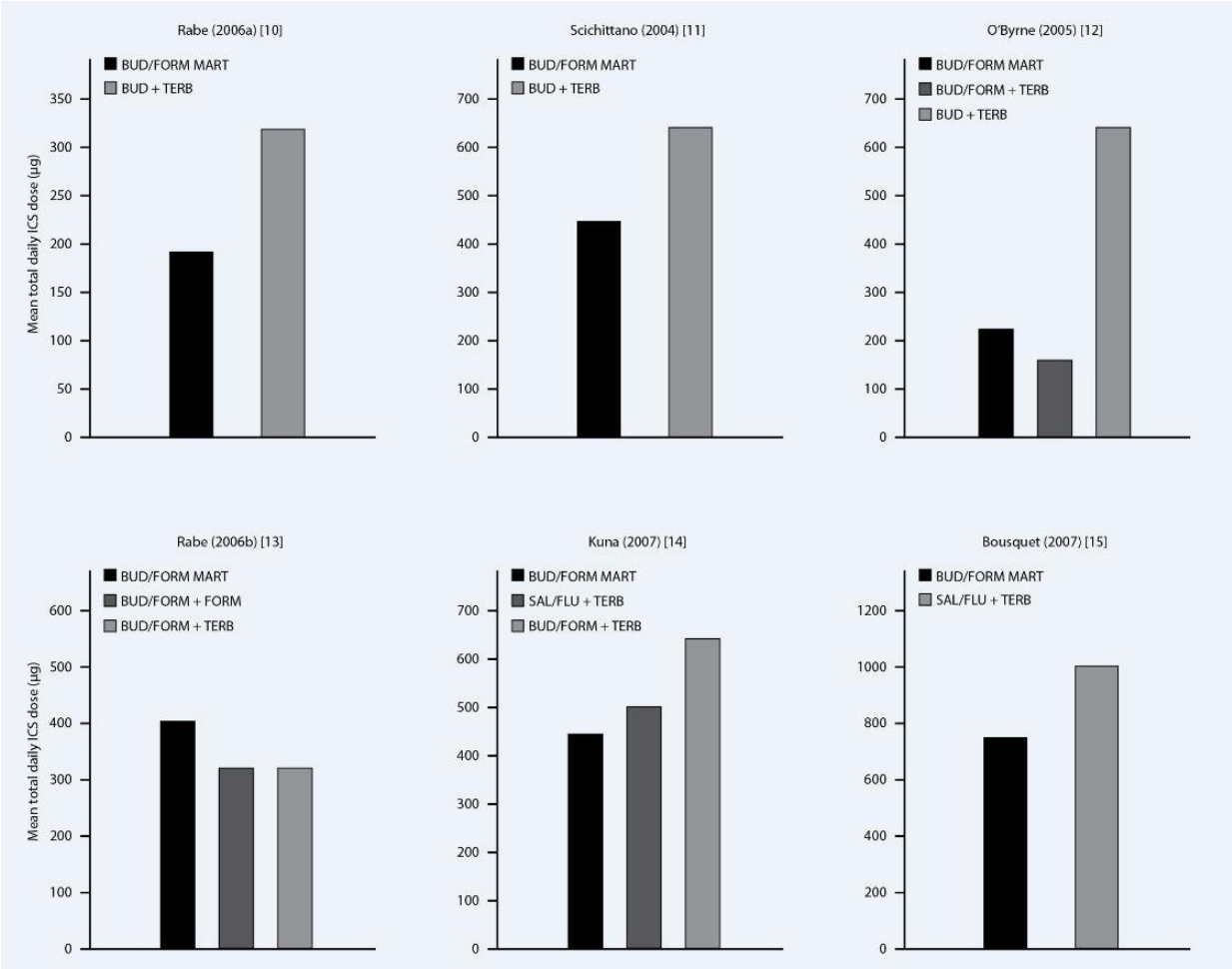
BUD, budesonide; FLU, fluticasone; FORM, formoterol; BUD/FORM, budesonide/formoterol; MART, maintenance and reliever therapy; SAL, salmeterol; SAL/FLU, salmeterol/fluticasone; TERB, terbutaline

*MedDRA version 18.0

**This table includes patients with AEs ongoing during randomised treatment and during the corresponding follow-up period. Patients with multiple AEs coded to the same preferred term were counted only once for that term.

[†]Events were sorted by the total for both columns

Figure S1. Mean total daily ICS dose in adolescents



BUD, budesonide; FLU, fluticasone; FORM, formoterol; ICS: inhaled glucocorticosteroid; MART, maintenance and reliever therapy; SAL, salmeterol; TERB, terbutaline.
All budesonide doses expressed as delivered dose. For the non-BUD/FORM MART arms total daily dose is the maintenance dose.

Full compliance is assumed for mean total daily ICS dose.