

Budesonide/Formoterol Anti-Inflammatory Reliever and Maintenance or Fluticasone Propionate/Salmeterol Plus As-Needed, Short-Acting β_2 Agonist: Real-World Effectiveness in Patients without Optimally Controlled Asthma (REACT) Study

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Shih-Lung Cheng,^{1,2} Ming-Lin Ho,³ Yun-Fa Lai,⁴ Hao-Chien Wang,⁵ Jeng-Yuan Hsu,⁶ Shih-Feng Liu,^{7,8} Ming-Shyang Huang,⁹ Cheng-Hung Lee,¹⁰ Ching-Hsiung Lin,^{3,11} Liang-Wen Hang,^{12,13} Yu-Chih Liu,¹⁴ Kuang-Yao Yang,^{15,16*} Jia-Horng Wang^{14,17,*}

¹Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; ²Department of Chemical Engineering and Materials Science, Yuan-Ze University, Taoyuan, Taiwan; ³Division of Chest Medicine, Kuang Tien General Hospital, Taichung, Taiwan; ⁴Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan; ⁵Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; ⁶Division of Clinical Research, Taichung Veterans General Hospital, Taichung, Taiwan; ⁷Department of Respiratory Therapy, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; ⁸Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; ⁹Department of Internal Medicine, E-DA Cancer Hospital and Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ¹⁰Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; ¹¹Division of Chest Medicine, Changhua Christian Hospital, Changhua, Taiwan; ¹²School of Nursing & Graduate Institute of Nursing, China Medical University, Taichung, Taiwan; ¹³Sleep Medicine Center, China Medical University Hospital, Taichung, Taiwan; ¹⁴Department of Internal Medicine, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan; ¹⁵Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ¹⁶Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; ¹⁷Hyperbaric Oxygen Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan

*These authors contributed equally to this work

Introduction: In the prospective, observational, 16-week REACT study conducted between October 21, 2008 and May 12, 2011, we compared the real-world effectiveness of anti-inflammatory reliever and maintenance therapy with budesonide/formoterol (Symbicort[®] Turbuhaler) and maintenance therapy with fixed-dose fluticasone/salmeterol (Seretide[®]) plus as-needed, short-acting β_2 agonists (SABAs) in Taiwanese patients with inadequate asthma control.

Methods: Asthma control was assessed using the five-item Asthma Control Questionnaire (ACQ-5) and standardized pulmonary function testing. Assessments were performed at baseline and at weeks 4–5 and 12–16. Overall, we enrolled 842 patients at 11 clinics, 723 of whom were included in analyses (budesonide/formoterol, 563.3±1.3 $\mu\text{g}/\text{d}$, n=551; fluticasone/salmeterol, 1013.8±1.4 $\mu\text{g}/\text{d}$, n=172).

Results: At baseline, 72.5% and 27.5% of all patients had “partly” and “uncontrolled” asthma, respectively. Mean±SD ACQ-5 scores were 1.54±1.06 and 1.46±1.28 in the budesonide/formoterol and fluticasone/salmeterol groups, respectively. ACQ-5 scores significantly improved from baseline (ie, decreased) in both groups at weeks 4 and 16. ACQ-5 difference scores were significantly lower in the budesonide/formoterol group (−0.91±1.11) than the fluticasone/salmeterol group (−0.69±1.27) at the end of the study (p=0.027). Peak expiratory flow rate significantly improved from baseline in the budesonide/formoterol but not the fluticasone/salmeterol group at the end of the study. Severe exacerbation rates and medical resource utilization were comparable between the budesonide/formoterol and fluticasone/salmeterol groups.

Conclusion: Collectively, results indicate the real-world effectiveness of budesonide/formoterol anti-inflammatory reliever and maintenance therapy is better than fixed-dose fluticasone/salmeterol plus as-needed SABA.

Trial Registration: ClinicalTrials.gov registration number: NCT00784953.

Keywords: budesonide/formoterol, fluticasone propionate/salmeterol, anti-inflammatory reliever and maintenance, real-world

Correspondence: Kuang-Yao Yang;
Jia-Horng Wang
Tel +886-2-28757455
Fax +886-2-28757610
Email kyyang@vghtpe.gov.tw; jiahorng.wang@gmail.com

Introduction

The 2006 Global Initiative for Asthma (GINA) report included major changes in asthma treatment strategies, with an emphasis on achieving and maintaining asthma control in most patients.¹ In the report, asthma was classified into three levels based

on the level of control and severity, and five treatment steps were delineated. Since then, recommendations have been refined and the latest GINA report update was published in 2020.² After assessing and correcting the common problems (such as inhaler technique and comorbidities), a step-up approach should be considered for patients with persistent symptoms and/or exacerbations. Nevertheless, the results of various studies over the last decade indicate that asthma control remains suboptimal despite ongoing asthma maintenance treatment.^{3–5} For example, among 3415 physician-recruited, adult asthma patients on regular maintenance therapy with inhaled corticosteroids (ICS) or ICS plus long-acting β_2 agonists (LABA) in the International Asthma Patient Insight Research (INSPIRE) study, 21% and 51% had not well controlled or uncontrolled asthma, respectively.³ And, in the cross-sectional REcognise Asthma and LInk to Symptoms and Experience (REALISE) study, wherein improvement in asthma control was evaluated using an online survey of 8000 adult asthma patients from 11 European countries, 35% and 45% of respondents had partly or uncontrolled asthma, respectively.⁵ Further, in a nationwide questionnaire-based survey among 3069 asthmatic patients from China, 45% and 26% of patients had partly controlled or uncontrolled asthma, respectively.⁴

In controlled studies, concomitant treatment with an ICS and LABA administered using a combination inhaler was more effective than treatment with only ICS using a step-up approach.^{6,7} Patients who received concomitant treatment showed significant improvements in symptoms and pulmonary function^{6,7} and achieved more rapid asthma control⁶ than controls. The “two-in-one” inhaler also benefits patients because of its convenience⁶ and thus may improve medication adherence.⁸ Fixed-combination inhaler therapies, such as Symbicort[®] Turbuhaler (AstraZeneca), which contains budesonide and the fast-acting LABA formoterol, and Seretide[®] (GSK), which contains fluticasone and salmeterol, are now recommended options for patients with moderate-to-severe asthma per GINA steps 3 and 4.¹

Kew and colleagues conducted a meta-analysis in which they assessed the efficacy and safety of anti-inflammatory reliever and maintenance therapy with budesonide/formoterol versus regular maintenance therapy with higher-dose ICS (budesonide/formoterol or fluticasone/salmeterol) plus short-acting β_2 agonists (SABAs) as a reliever medication when needed among adults and

children with chronic asthma.⁹ Four studies randomly assigning 9,130 patients with asthma were included. The quantity of ICS, including as-needed inhalations taken for symptom relief, was consistently lower in budesonide/formoterol combination patients than comparison groups.⁹ Additionally, fewer patients using anti-inflammatory reliever and maintenance therapy had severe exacerbations requiring emergency department (ED) visits or hospitalization than higher-dose regular medication plus SABA, and fewer had exacerbations requiring a course of oral corticosteroids.

The true benefits of different treatments on asthma control cannot necessarily be realized entirely through clinical trial results because of the rigor of patient selection and trial conduct.¹⁰ For example, trial participants are more likely to be adherent with medication than patients in real-world clinical practice. Poor compliance and concomitant disease are the primary barriers to adequate treatment for patients with asthma, and these factors can negatively impact asthma control in real life. Limited comparative data, particularly real-world data, are available for budesonide/formoterol as anti-inflammatory reliever and maintenance versus fixed-dose fluticasone/salmeterol plus as-needed SABA.^{11–13} In this non-interventional, all-comer study, we investigated the real-world effectiveness of anti-inflammatory reliever and maintenance therapy with budesonide/formoterol compared with maintenance therapy with fluticasone/salmeterol plus as-needed SABA among Taiwanese patients with inadequate asthma control.

Materials and Methods

Study Design

Real-world Effectiveness in pAtients without optimally Controlled asThma (REACT) was a prospective, observational, 16-week cohort study conducted between October 21, 2008 and May 12, 2011 at 11 pulmonary outpatient clinics at local hospitals throughout Taiwan. The study, which was conducted in compliance with the Declaration of Helsinki for observational studies and was approved by the Institutional Review Boards of all participating centres, was designed to mimic routine clinical practice, enabling assessment of effectiveness of the study drugs in a real-world environment. Written informed consent was obtained from all patients before study participation.

Ethics

Before any patients were enrolled, an independent ethics committee or institutional review board at each study center approved the clinical study protocol. (97083, Research Ethics Review Committee Far Eastern Memorial hospital; 081025, Institutional board review Committee A, Changhua Christian Hospital; 200809049R, Research Ethics Review Committee National Taiwan University Hospital; S08194#3, Institutional Review Board TCVGH; 97-2115A3, Research Ethics Review Committee CGMH; ER-97-176, Institutional Review Board Cheng Kung University Hospital; DMR97-IRB-218-2, Institutional Review Board China Medical University; 97-11-13A#1, Institutional Review Board TPVGH). All patients provided written informed consent at enrollment. Each study was conducted in accordance with the principles of the Declaration of Helsinki/Good Clinical Practice guidelines. The authors are not willing to share the related data of the patients enrolled in this study. Therefore, there has no specific data or documents to be shared or available.

Study Population and Treatments

Patients were enrolled if they were diagnosed with asthma for ≥ 6 months, had partly controlled or uncontrolled asthma,¹ were taking only ICS or low-dose ICS plus a LABA, leukotriene modifier, or theophylline. Patients taking lower dose study drugs at baseline were permitted to step up to higher doses per GINA recommendations if required. Patients were excluded if they were participating in or had been enrolled in a clinical trial within 12 weeks of enrollment, had contraindications to ICS/LABA fixed-dose combinations (FDC), were taking oral corticosteroids within 4 weeks of enrollment, or were pregnant.

Data Collection and Assessments

Principal and co-investigators collected effectiveness data from consecutive outpatients at each clinic using case report forms. Patient diary cards were collected and patient education to optimize adoption of various devices/inhalers was provided, based on materials routinely used in clinics. Criteria for the varying degrees of asthma control were as presented in the 2006 GINA report.¹ For assessment of asthma control, patients completed a Chinese for Taiwan version of the five-item Asthma Control Questionnaire (ACQ-5). An ACQ-5 score of ≤ 0.75 , 0.75 to 1.5, and ≥ 1.5 defined controlled, partly controlled, and uncontrolled asthma, respectively.¹⁴

For assessment of lung function, standardized pulmonary function testing, including forced expiratory volume in one second (FEV₁) and peak expiratory flow rate (PEFR), were performed. All assessments were completed at baseline, at 4 to 5 weeks after study drug initiation (assessment visit 1), during Weeks 12–16 (assessment visit 2), and at end of study (Week 16). Demographic data, severe exacerbation frequency, previous and ongoing asthma therapies, adherence, healthcare resource utilization (hospitalizations, ED admissions, and medical consultations), and daily amounts of ICS used per budesonide base ($\mu\text{g}/\text{d}$) for asthma during the 3 months were collected before initiation/step-up of study medication and/or throughout the study.

Statistical Analysis

A 5% significance level using a two-sided alternative hypothesis and power of 90% were used for sample size calculations. With an expected dropout rate of 20%, a total of 380 patients each in the budesonide/formoterol anti-inflammatory reliever and maintenance group were required to detect improvements in ACQ-5 score from baseline based on changes of 0.5 points.

The analyses were based on an ITT approach using the full analysis set (FAS) including all patients who received ≥ 1 dose of the study drug and had a post-treatment visit (with ≥ 1 effectiveness assessment), regardless of compliance with the protocol. For some patients, assessment visits 1 and 2 did not occur during the protocol-defined times (4–5 weeks and 12–16 weeks, respectively). Thus, some discrepancies occurred in number of patients assessed at these time points. However, all data available at the assessment visit 2 were included in the “end-of-study” analyses. For analysis of ACQ-5 scores and lung function tests, only patients with baseline and corresponding post-treatment data were included. No missing value imputation was performed for post-treatment assessment.

A Chi-square test was used for categorical variables, and an unpaired *t*-test was used for continuous variables. Differences in ACQ-5 scores, FEV₁, and PEFR between mean baseline values and values at assessment time points for each treatment were compared using Student’s paired *t*-tests. Changes from baseline in FEV₁ and PEFR were also compared using Student’s paired *t*-tests. Patient adherence was defined as the percentage of days that a prescription was followed during the evaluation period based on patient diary data. For all statistical analyses, a probability value of <0.05 was considered statistically

significant, with no adjustments made for multiplicity. For FEV₁ a change of 0.10–0.20 L is considered to be the minimal important difference (MID).¹⁵ On the ACQ-5 scale, a change in score of 0.5 is considered to be the MID¹⁶ and would justify a change in a patient's treatment.¹⁶

Results

Patient Disposition, Demographics, and Clinical Characteristics

We enrolled 842 asthma patients. Seventeen patients who did not receive study drug and 102 patients without at least one effectiveness assessment were excluded. Therefore, the FAS comprised 723 patients: 551 patients in the budesonide/formoterol anti-inflammatory reliever and maintenance group and 172 in the fluticasone/salmeterol group. Asthma treatment adherence in both groups was high (approximately 90%), and only around 3% of patients had their asthma treatments changed during this study.

In the FAS, 48.1% of patients were male and 51.9% were female (Table 1). Demographics and baseline characteristics of patients were similar between treatment groups, except for age (mean±SD age of 55.3±16.1 [budesonide/formoterol] versus 59.4±17.5 years [fluticasone/salmeterol]). Overall, 72.5% of patients had partly controlled asthma (74.0% and 67.4%, respectively), and 27.5% had uncontrolled asthma (26.0% and 32.6%, respectively) according to GINA. Incidence of severe exacerbations within 3 months of enrollment was 1.05±2.99 overall (budesonide/formoterol, 1.09±3.23; fluticasone/salmeterol, 0.90±2.02), and mean±SD ACQ-5 score was 1.52±1.11 overall (1.54±1.06 and 1.46±1.28, respectively).

Effectiveness

ACQ-5 Scores

Overall, ACQ-5 score significantly decreased (ie, improved) from 1.52±1.11 at baseline to 0.73±0.87 at Week 4, and further decreased to 0.62±0.78 at Weeks 12–16 (Table 2). Mean change from baseline in ACQ-5 score was –0.76 at Week 4 (n=454) and –0.81 at Weeks 12–16 (n=247), and clinically meaningful (>0.50). Generally, asthma control improved by Week 4. Moreover, by the end of the study, the decrease in change from baseline ACQ-5 scores was significantly larger in the budesonide/formoterol group (–0.91±1.11) than the fluticasone/salmeterol group (–0.69±1.27; p=0.027), although it did not reach the minimal important difference (MID). Significantly more patients had

controlled asthma in the budesonide/formoterol group than the fluticasone/salmeterol group (56.1% versus 43.6%, p=0.004, Table 3).

Lung Function

Out of the 771 included patients, 305 had lung function measurements at baseline. In the budesonide/formoterol group (252 patients), mean FEV₁ increased from 1.82±0.77 L at baseline to 1.85±0.75 L at the end of the study. However, in the fluticasone/salmeterol subgroup (53 patients), the mean FEV₁ decreased from 1.54±0.72 L at baseline to 1.31±0.75 L by the end of the study so the difference between treatments was clinically relevant (Table 4). Moreover, relative to baseline, PEFR significantly increased for patients who received budesonide/formoterol (263 patients, 310.8±126.0 L/min versus 349.8±133.6 L/min, p<0.001). A small increase in PEFR was also found in the fluticasone/salmeterol subgroup (65 patients, 279.4±109.7 L/min versus 281.4±123.2 L/min, p=0.474), although this was not statistically significant (Table 5).

Severe Exacerbations and Medical Resource Utilization

During the study, 54 severe exacerbations occurred (36.7 events/100 person-years [PY]), comprising 43 unscheduled clinical visits (29.3 events/100 PY); 4 ED visits (2.7 events/100 PY), 5 hospitalizations (3.4 events/100 PY), and 12 oral steroid treatment uses (8.2 events/100 PY) (Table 6). The incidence of severe exacerbation events was not significantly different between budesonide/formoterol- and fluticasone/salmeterol-treated patients.

Daily ICS Use

Mean daily ICS dosage for patients in the budesonide/formoterol anti-inflammatory reliever and maintenance group was significantly lower than for the fluticasone/salmeterol group (563.3±1.3 µg/d versus 1013.8±1.4 µg/d, p<0.001).

Discussion

According to GINA, the primary goal of asthma management is to achieve and maintain asthma control (minimize symptoms, activity limitations, bronchoconstriction, and rescue SABA use) and, thus, reduce the future risks of life-threatening exacerbations and long-term morbidity.^{1,2} In this real-world study, treatment with ICS/LABA combined therapies (budesonide/formoterol and fluticasone/salmeterol) significantly improved asthma control as early as 4 weeks after treatment initiation among patients with partly

Table 1 Patient Demographic and Clinical Characteristics

	Total N = 723	Budesonide/ Formoterol MART n = 551	Fluticasone/Salmeterol Plus As-Needed SABA n = 172	p-value
Gender, n (%)				
Male	348 (48.1)	269 (48.8)	79 (45.9)	0.508
Female	375 (51.9)	282 (51.2)	93 (54.1)	
Age, years				
Mean (SD)	56.3 (16.6)	55.3 (16.1)	59.4 (17.5)	0.004
Min–Max	11.5–93.5	14.2–93.5	11.5–90.3	
Height, cm				
Mean (SD)	160.8 (8.4)	161.1 (8.3)	159.7 (8.6)	0.064
Min–Max	136.0–193.0	136.0–183.0	140.0–193.0	
Weight, Kg				
Mean (SD)	64.5 (12.0)	64.9 (12.1)	63.3 (11.6)	0.137
Min–Max	37.5–113.0	37.5–113.0	41.0–100.0	
BMI, Kg/m²				
Mean (SD)	24.9 (4.0)	25.0 (4.0)	24.8 (3.9)	0.611
Min–Max	15.6–42.0	16.0–42.0	15.6–40.1	
Level of asthma control at enrollment, n (%)				
Partly controlled	524 (72.5)	408 (74.0)	116 (67.4)	0.090
Uncontrolled	199 (27.5)	143 (26.0)	56 (32.6)	
Medical events (within 3 months prior to enrollment)				
Number of severe exacerbations				
Mean (SD)	1.05 (2.99)	1.09 (3.23)	0.90 (2.02)	0.459
n (%)	236 (32.6)	169 (30.7)	67 (39.0)	0.043
Number of unscheduled clinical visits				
Mean (SD)	0.35 (1.15)	0.33 (1.16)	0.42 (1.12)	0.370
n (%)	120 (16.6)	82 (14.9)	38 (22.1)	0.026
Number of emergency department visits				
Mean (SD)	0.09 (0.35)	0.10 (0.37)	0.08 (0.27)	0.590
n (%)	58 (8.0)	44 (8.0)	14 (8.1)	0.948
Number of hospitalizations				
Mean (SD)	0.03 (0.20)	0.03 (0.20)	0.04 (0.20)	0.444
n (%)	19 (2.6)	12 (2.2)	7 (4.1)	0.178

Note: Bold font indicates statistical significance.

Abbreviations: ACQ-5, five-item Asthma Control Questionnaire; BMI, body mass index; MART, anti-inflammatory reliever and maintenance therapy; SABA, short-acting β_2 agonist; SD, standard deviation.

controlled or uncontrolled asthma. In addition, ACQ-5 scores were lower and lung function test results were improved with budesonide/formoterol anti-inflammatory reliever and maintenance compared with fluticasone/salmeterol treatment.

Results of previous clinical trials demonstrate consistent, marked reductions in asthma exacerbations and rescue medication use over time when patients used budesonide/formoterol anti-inflammatory reliever and maintenance therapy versus traditional FDC therapies

with as-needed SABA as reliever.^{17–22} In our study, the real-world effectiveness of budesonide/formoterol maintenance and anti-inflammatory reliever versus fluticasone/salmeterol plus as-needed SABA was evaluated during a 16-week period among 723 Taiwanese patients with partly controlled or uncontrolled asthma despite ongoing therapies. At baseline, the overall mean ACQ-5 score was 1.52 ± 1.11 , which indicated poorly controlled asthma in this study population. At the end of the study, the overall mean ACQ-5 score improved significantly to 0.66 ± 0.84

Table 2 Summary of ACQ-5 Scores (Full Analysis Set)

	Total	Budesonide/Formoterol	Fluticasone/Salmeterol	p-value (Between Study Groups)*
Baseline				
n	722	550	172	
Mean (SD)	1.52 (1.11)	1.54 (1.06)	1.46 (1.28)	
Week 4 (Days 28–34)				
n	454	343	111	
Mean (SD)	0.73 (0.87)	0.72 (0.85)	0.78 (0.92)	0.504
Mean (SD) change from baseline	−0.76 (1.12)	−0.78 (1.07)	−0.68 (1.26)	
Weeks 12–16 (Days 84–111)				
n	247	178	69	
Mean (SD)	0.62 (0.78)	0.57 (0.74)	0.74 (0.86)	0.111
Mean (SD) change from baseline	−0.81 (1.18)	−0.83 (1.04)	−0.73 (1.50)	
End of study				
n	719	547	172	
Mean (SD)	0.66 (0.84)	0.63 (0.80)	0.77 (0.95)	0.056
Mean (SD) change from baseline	−0.86 (1.15)	−0.91 (1.11)	−0.69 (1.27)	

Note: *Two-sided t-test without adjustments.

Abbreviations: ACQ-5, five-item Asthma Control Questionnaire; SD, standard deviation.

Table 3 Asthma Control Status (Full Analysis Set)

	Total	Budesonide/Formoterol	Fluticasone/Salmeterol	p-value
Baseline				
n	723	551	172	0.090 ⁺
Partly controlled	524 (72.5%)	408 (74.0%)	116 (67.4%)	
Uncontrolled	199 (27.5%)	143 (26.0%)	56 (32.6%)	
Week 4 (Days 28–34)				
n	454	343	111	0.194 ⁺
Controlled	199 (43.8%)	156 (45.5%)	43 (38.7%)	0.213*
Partly controlled	221 (48.7%)	159 (46.4%)	62 (55.9%)	
Uncontrolled	34 (7.5%)	28 (8.2%)	6 (5.4%)	
Weeks 12–16 (Days 84–111)				
n	250	181	69	0.183 ⁺
Controlled	156 (62.4%)	119 (65.7%)	37 (53.6%)	0.077*
Partly controlled	82 (32.8%)	54 (29.8%)	28 (40.6%)	
Uncontrolled	12 (4.8%)	8 (4.4%)	4 (5.8%)	
End of study				
n	723	551	172	0.014 ⁺
Controlled	384 (53.1%)	309 (56.1%)	75 (43.6%)	0.004*
Partly controlled	299 (41.4%)	212 (38.5%)	87 (50.6%)	
Uncontrolled	40 (5.5%)	30 (5.4%)	10 (5.8%)	

Notes: Bold font indicates statistical significance. ⁺Comparison of asthma control status distribution between the two treatment groups. *Comparison of controlled rate between the two treatment groups.

($p < 0.001$). Significant relief of asthma symptoms was observed as early as Week 4 of treatment with budesonide/formoterol treatment and persisted through Week 16

of treatment. Overall, patients in both treatment groups experienced significant improvement in ACQ-5 scores and asthma control, though the ACQ-5 score

Table 4 Forced Expiratory Volume in 1 Second (FEV₁) Results (Full Analysis Set)

(Unit: L)	Total	Budesonide/Formoterol	Fluticasone/Salmeterol	p-value
Baseline				
n	305	252	53	
Mean (SD)	1.77 (0.77)	1.82 (0.77)	1.54 (0.72)	0.016
Week 4 (Days 28–34)				
n	60	45	15	
Mean (SD)	1.71 (0.72)	1.83 (0.69)	1.34 (0.70)	0.021
Mean (SD) change from baseline	0.01 (0.37)	0.03 (0.35)	−0.06 (0.48)	0.560
p-value (change from baseline)	0.875	0.671	0.726	
Weeks 12–16 (Days 84–111)				
n	39	28	11	
Mean (SD)	1.60 (0.86)	1.81 (0.88)	1.08 (0.54)	0.004
Mean (SD) change from baseline	−0.04 (0.37)	−0.02 (0.32)	−0.13 (0.56)	0.481
p-value (change from baseline)	0.538	0.803	0.555	
End of study				
N	86	66	20	
Mean (SD)	1.72 (0.78)	1.85 (0.75)	1.31 (0.75)	0.006
Mean (SD) change from baseline	0.07 (0.38)	0.09 (0.36)	−0.01 (0.48)	0.420
p-value (change from baseline)	0.109	0.061	0.957	

Note: Bold font indicates statistical significance.

Abbreviation: SD, standard deviation.

Table 5 Peak Expiratory Flow Rate (PEFR) Results (Full Analysis Set)

(Unit: L/min)	Total	Budesonide/Formoterol	Fluticasone/Salmeterol	p-value
Baseline				
N	328	263	65	
Mean (SD)	304.6 (123.4)	310.8 (126.0)	279.4 (109.7)	0.066
Week 4 (Days 28–34)				
N	132	99	33	
Mean (SD)	341.8 (134.4)	362.0 (141.0)	281.2 (89.8)	<0.001
Mean (SD) change from baseline	29.4 (89.2)	35.7 (87.1)	12.7 (94.1)	0.265
p-value (change from baseline)	0.002	0.001	0.498	
Weeks 12–16 (Days 84–111)				
N	86	62	24	
Mean (SD)	323.5 (134.1)	347.3 (136.7)	262.2 (107.0)	0.008
Mean (SD) change from baseline	9.1 (77.5)	15.1 (73.2)	−5.6 (87.5)	0.344
p-value (change from baseline)	0.358	0.178	0.791	
End of Study				
N	179	135	44	
Mean (SD)	333.0 (134.1)	349.8 (133.6)	281.4 (123.2)	0.003
Mean (SD) change from baseline	21.5 (73.1)	24.5 (67.8)	11.6 (89.2)	0.391
p-value (change from baseline)	0.001	<0.001	0.474	

Note: Bold font indicates statistical significance.

Abbreviation: SD, standard deviation.

improvements in the fluticasone/salmeterol treatment group were not as large as in the budesonide/formoterol anti-inflammatory reliever and maintenance group.

Further, PEFR levels, but not FEV₁ levels, significantly improved from baseline after initiating budesonide/formoterol therapy, indicating improvement in lung function, particularly

Table 6 Severe Exacerbations and Medical Resource Utilization: Patient- and Event-Based Rates (95% Confidence Intervals) per 100 Patient-Years (Full Analysis Set)

	Total N = 723	Budesonide/Formoterol n = 551	Fluticasone/Salmeterol n = 172
Exacerbations			
Patient-based	23.8 (16.6–33.1)	26.4 (17.7–37.9)	16.1 (5.9–35.1)
Event-based	36.7 (27.6–47.9)	37.3 (26.8–50.7)	34.9 (18.6–59.8)
Unscheduled clinic visits (number)			
Patient-based	16.3 (10.5–24.3)	19.1 (11.8–29.2)	8.1 (1.6–23.6)
Event-based	29.3 (21.2–39.4)	30.1 (20.7–42.2)	26.9 (12.9–49.4)
Emergency department visits (number)			
Patient-based	2.7 (0.7–7.0)	1.8 (0.2–6.6)	5.4 (0.6–19.4)
Event-based	2.7 (0.7–7.0)	1.8 (0.2–6.6)	5.4 (0.6–19.4)
Hospitalizations (number)			
Patient-based	3.4 (1.1–7.9)	3.6 (1.0–9.3)	2.7 (0.4–15.0)
Event-based	3.4 (1.1–7.9)	3.6 (1.0–9.3)	2.7 (0.4–15.0)
Oral corticosteroid treatment (number)			
Patient-based	5.4 (2.3–10.7)	4.6 (1.5–10.6)	8.1 (1.6–23.6)
Event-based	8.2 (4.2–14.3)	5.5 (2.0–11.9)	16.1 (5.9–35.1)

of large airways ($p < 0.001$ for change in PEFR at end of the study). As with ACQ-5 scores, improvements in lung function, as determined by PEFR results, were apparent as early as Week 4 after initiating budesonide/formoterol anti-inflammatory reliever and maintenance therapy and persisted through Week 16 of treatment. Overall lung function, as determined by PEFR and FEV₁ results, was better in budesonide/formoterol-treated than fluticasone/salmeterol-treated patients. All measured variables indicated that budesonide/formoterol anti-inflammatory reliever and maintenance therapy was associated with significant improvements from baseline that was at least comparable with, if not higher than, fluticasone/salmeterol regular maintenance plus as-needed SABA in this real-world study. Our results are similar to those of Zhong and colleagues who found that treatment of inadequately controlled asthmatic patients with budesonide/formoterol anti-inflammatory reliever and maintenance therapy resulted in significant improvement in patients' asthma control and reductions in asthma symptoms and as-needed medication use.¹²

Results of other assessments also support the substantial benefit of budesonide/formoterol as anti-inflammatory reliever and maintenance therapy. The average daily ICS dosage for patients in the budesonide/formoterol group was nearly half that for the fluticasone/salmeterol group. A previous clinical appraisal that compared anti-inflammatory reliever and maintenance therapy and fixed-dose regimens reported improvements that were attributed

to patients who received additional ICS therapy administered in response to symptom requirements.¹⁹ However, in the present real-world study and previous studies,^{13,23–25} the average amount of ICS used was lower for patients who received budesonide/formoterol than a conventional fixed-dose strategy, even though better treatment efficacy and health benefits were achieved. This is most likely explained by appropriate and timely ICS use with budesonide/formoterol anti-inflammatory reliever and maintenance therapy, which meets patients' expectations for effectiveness and simplifies their treatment in terms of a single inhaler. This is also consistent with the recommendations made in the GINA guidelines.² In 2019, the update of the GINA report recommended ICS/formoterol therapy as the preferred reliever across all steps of the treatment algorithm, except for patients treated with an ICS/LABA that does not contain formoterol as the LABA.² This change was mainly based on evidence from the SYGMA I study showing that as-needed budesonide/formoterol provided superior asthma symptom control and reduced exacerbation rate compared with as-needed SABA in mild asthma.²⁶ The anti-inflammatory reliever and maintenance concept has also been shown to provide better efficacy across a range of asthma severities.^{27–31} In a review article, Jenkins et al confirmed that patients with asthma treated with budesonide/formoterol anti-inflammatory reliever and maintenance therapy achieved the same or better symptom control compared

with ICS/LABA plus SABA therapy at similar or higher ICS doses.²⁹ Jenkins et al also found that maintenance dosing ensured day-to-day control, and the use of a reliever with anti-inflammatory properties provides extra doses of ICS as soon as symptoms prompt the use of reliever.²⁹ These findings from previous key studies of budesonide/formoterol anti-inflammatory reliever and maintenance therapy are consistent with our findings in this study.

No significant differences in severe exacerbation rates and medical resource utilization were observed between treatment groups in the FAS. Further large-scale studies with long-term follow-up may be needed to confirm the beneficial effects of budesonide/formoterol anti-inflammatory reliever and maintenance therapy, specifically in Asian populations.

Some limitations of our study should be acknowledged. This study was not randomized or controlled; sample sizes were different between the two treatment groups; safety was not assessed; some patients were already under Symbicort or Seretide treatment before they are enrolled in this study; some significant between-group differences existed in baseline characteristics; and follow-up was irregular; and the evaluation period was relatively short (16 weeks). Some or all of these limitations may have contributed to the better asthma control and lower ACQ-5 scores observed in the budesonide/formoterol maintenance and anti-inflammatory reliever group. However, these limitations highlight the real-world challenges in the management of asthma. We sought to enroll a wide range of patients with inadequately controlled asthma to evaluate the effectiveness of treatments in daily clinical practice and to truly portray real-world asthma control in patients with moderate-to-severe asthma.

In conclusion, during real-world treatment of Taiwanese patients with inadequately controlled asthma, treatment with Symbicort Turbuhaler (budesonide/formoterol) as anti-inflammatory reliever and maintenance therapy was associated with significant improvements in ACQ-5 scores, asthma control, and pulmonary function (PEFR). These improvements were comparable with, if not better than, a fixed-dose regimen of fluticasone/salmeterol plus as-needed SABA (mean daily ICS dose for patients in each group was different). Medical resource utilization, including oral corticosteroid use, was comparable between treatment groups.

Clinical Trial Registration

This study was registered at www.ClinicalTrials.gov with clinical trial identifier no. NCT00784953.

Acknowledgments

Medical writing and/or editorial assistance in the form of assembling tables, collating author comments, copyediting, fact checking, and referencing based on authors' detailed directions, was provided by Vidula Bhole, MD, MHSc, Shruti Baijal Ph.D. and Maribeth Bogush, MCI, PhD of Cactus Communications. This assistance was funded by AstraZeneca Taiwan. The authors retained full control of the manuscript content.

Funding

AstraZeneca Taiwan.

Disclosure

The REACT study was supported by AstraZeneca Taiwan. The authors declare that there are no additional conflicts of interest.

References

- Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Resp J.* 2008;31(1):143–178. doi:10.1183/09031936.00138707
- Global strategy for asthma management and prevention; 2020. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_final_wms.pdf. Accessed May 15, 2020.
- Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the Inspire study. *BMC Pulm Med.* 2006;6(1):13. doi:10.1186/1471-2466-6-13
- Su N, Lin J, Chen P, et al. Evaluation of asthma control and patient's perception of asthma: findings and analysis of a nationwide questionnaire-based survey in China. *J Asthma.* 2013;50(8):861–870. doi:10.3109/02770903.2013.808346
- Price D, Fletcher M, van der Molen T. Asthma control and management in 8000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med.* 2014;24(1):14009. doi:10.1038/nppcr.2014.9
- Kuna P, Creemers JP, Vondra V, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. *Respir Med.* 2006;100(12):2151–2159. doi:10.1016/j.rmed.2006.03.016
- Laloo UG, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest.* 2003;123(5):1480–1487. doi:10.1378/chest.123.5.1480
- Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol.* 2004;113(2):245–251. doi:10.1016/j.jaci.2003.10.011
- Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2013;12:CD009019.
- Barnes NC. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med.* 2004;170(8):830–831. doi:10.1164/rccm.2408006

11. Tunceli O, Williams SA, Kern DM, et al. Comparative effectiveness of budesonide-formoterol combination and fluticasone-salmeterol combination for asthma management: a United States retrospective database analysis. *J Allergy Clin Immunol Pract.* 2014;2(6):719–726. doi:10.1016/j.jaip.2014.07.016
12. Zhong N, Lin J, Mehta P, Ngamjanyaporn P, Wu TC, Yunus F. Real-life effectiveness of budesonide/formoterol maintenance and reliever therapy in asthma patients across Asia: SMARTASIA study. *BMC Pulm Med.* 2013;13:22.
13. Kardos P. Budesonide/formoterol maintenance and reliever therapy versus free-combination therapy for asthma: a real-life study. *Pneumologie.* 2013;67(8):463–470. doi:10.1055/s-0033-1344349
14. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying ‘well-controlled’ and ‘not well-controlled’ asthma using the asthma control questionnaire. *Respir Med.* 2006;100(4):616–621. doi:10.1016/j.rmed.2005.08.012
15. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol.* 2012;129(3):S65–S87. doi:10.1016/j.jaci.2011.12.986
16. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med.* 2005;99(5):553–558. doi:10.1016/j.rmed.2004.10.008
17. Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.* 2007;61(5):725–736. doi:10.1111/j.1742-1241.2007.01338.x
18. Vogelmeier C, D’Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J.* 2005;26(5):819–828. doi:10.1183/09031936.05.00028305
19. O’Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med.* 2005;171(2):129–136. doi:10.1164/rccm.200407-8840C
20. 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):744–753. doi:10.1016/S0140-6736(06)69284-2
21. Rabe KF, Pizzichini E, Stallberg B, 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):246–256. doi:10.1378/chest.129.2.246
22. Scicchitano R, Aalbers R, Ukena D, 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):1403–1418. doi:10.1185/030079904X2051
23. Quirce S, Barcina C, Plaza V, et al. A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain. *J Asthma.* 2011;48(8):839–847. doi:10.3109/02770903.2011.611954
24. 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):173–182. doi:10.1111/j.1752-699X.2010.00217.x
25. 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):1479–1488. doi:10.1111/j.1742-1241.2009.02185.x
26. O’Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med.* 2018;378(20):1865–1876. doi:10.1056/NEJMoa1715274
27. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β -agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *J Am Med Assoc.* 2018;319(14):1485–1496. doi:10.1001/jama.2018.2769
28. Beasley R, Braithwaite I, Semprini A, et al. ICS-formoterol reliever therapy stepwise treatment algorithm for adult asthma. *Eur Respir J.* 2020;55(1):1901407. doi:10.1183/13993003.01407-2019
29. Jenkins CR, Bateman ED, Sears MR, O’Byrne PM. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever? *Respirology.* 2020;10:1111.
30. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med.* 2019;380(21):2020–2030. doi:10.1056/NEJMoa1901963
31. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet.* 2019;394(10202):919–928. doi:10.1016/S0140-6736(19)31948-8

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also

been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>

Dovepress