Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

# Budesonide/Formoterol Anti-Inflammatory Reliever and Maintenance or Fluticasone Propionate/Salmeterol Plus As-Needed, Short-Acting $\beta_2$ Agonist: Real-World Effectiveness in pAtients without Optimally Controlled asThma (REACT) Study

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**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 $\beta_2$ 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 μg/d, n=551; fluticasone/salmeterol, 1013.8±1.4 μg/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

## 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 $\beta_2$ 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 control[6] than controls. The "two-in-one" inhaler also benefits patients because of its convenience[6] 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 $\beta_2$ 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 ($FEV_1$) 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 (μg/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, $FEV_1$, 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 $FEV_1$ 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 $FEV_1$ 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 MID[16] 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 $FEV_1$ 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 $FEV_1$ 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/m$^2$** | | | | |
| 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 $\beta_2$ 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 ($FEV_1$) 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 $FEV_1$ 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 $FEV_1$ 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.

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