

Original article

Cost-effectiveness of budesonide/formoterol maintenance and rescue therapy in Thailand

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Background: The prevalence of asthma has increased significantly in Thailand. Budesonide/formoterol maintenance and reliever therapy has been available for several years. However, cost-effectiveness of such treatment has never been examined in Thailand.

Objective: Design a cost-effectiveness (CE) analysis conducted from a Thai healthcare perspective as a piggyback study accompanying a recent clinical trial.

Methods: The CE analysis was conducted from the healthcare provider's perspective. Data were collected from a six-month, double-blind, multi-national study involving 3321 symptomatic asthma patients randomized to either: bud/form maintenance and reliever therapy, bud/form 320/9 µg bid plus terbutaline as needed, or salmeterol/fluticasone (salm/flut) 25/125 µg two inhalations bid plus terbutaline as needed. Efficacy was determined as the number of exacerbations per patient during a six-month period. Thai unit costs were collected from the national sources and expert opinions, and applied to the resource use data for a deterministic economic evaluation.

Results: There were significantly fewer exacerbations in the bud/form maintenance and reliever therapy (0.12 events/patient/6 months) group vs. the bud/form (0.16 events/patient/6 months, $p < 0.01$), or salm/flut groups (0.19 events/patient/6 months, $p < 0.001$). Total direct costs (healthcare visits and drug costs) were 27.0% and 5.9% lower in the bud/form maintenance and reliever therapy group than in the bud/form and salm/flut groups, respectively.

Conclusion: Bud/form maintenance and reliever therapy was associated with significantly fewer exacerbations, compared to other fixed combination treatments in a recent multi-national clinical trial. This might result in lower direct costs if applied to the Thai healthcare system.

Keywords: Asthma, budesonide, cost-effectiveness analysis, formoterol, Thailand

The number of asthma patients in Thailand is increasing. According to epidemiology studies by Vichayanond et al. [1-3], the prevalence of childhood asthma has increased markedly. Similar results were found in provincial children [4]. There is a nationwide cross-sectional survey of respiratory health to demonstrate that in people aged 20 to 44 years, the prevalence of bronchial hyper-responsiveness and definite asthma was 3.3% and 2.9%, respectively [5].

Recently, Boonsawat and Chareonphan [6] made a multicentre survey of adult asthma in four cities (Bangkok, Chiang Mai, Khon Kaen, and Songkhla) in

Thailand. The four areas were significantly burdened by the severity of asthma cases [7]. Approximately 15% of respondents were hospitalized during a one-year period. The treatment of patients with moderate to severe asthma with inhaled corticosteroids (ICS) was sub-optimal.

Cost-effectiveness (CE) analyses may provide further relevant information for clinicians when selecting treatment options for individual patients. A number of international studies on the CE analysis of treating asthma patients have been conducted [8-17]. However, only two cost-of-illness studies have examined the economic effects of asthma in Thailand [18, 19]. According to O'Bryne et al. [20], the budesonide/formoterol (bud/form) combination, given as both maintenance and reliever therapy, was more effective for reducing exacerbations and improving

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daily asthma control than the same maintenance dose of bud/form plus as-needed short-acting beta-agonist. Patients who received bud/form as both maintenance and reliever used, on average, a higher daily dose of bud/form than did patients who received the fixed-dose bud/form regimen. Subsequently, Kuna et al [21] demonstrated that the bud/form maintenance and reliever therapy regimen was associated with the lowest exacerbation rate, even if all treatments provides similar marked improvements in lung function, thus better daily asthma control and asthma-related quality-of-life.

The economic evaluation of treatment choices is pivotal to improving asthma treatment in Thailand. In this study, we designed a CE analysis as a piggyback study to the multi-national study. In addition, the budget-impact analysis in terms of savings among alternative treatments was estimated.

Materials and methods

The CE analysis was designed as a piggyback economic evaluation alongside a multi-national six-month, double-blind, randomized, parallel-group clinical trial (study code SD-039-0735) accordingly to the previous report by Kuna et al. [21]. Adults (>18 years) and adolescents (12-17 years) with persistent asthma who were symptomatic despite regular use of ICS with a predicted mean forced expiratory volume in one second (FEV_1) of 73.0% and a mean ICS dose 745 $\mu\text{g}/\text{day}$ were eligible for inclusion in the parent study. Patients attended the clinic at the beginning and end of a two-week run-in period (visits 1 and 2) during which patients used their regular ICS for maintenance and terbutaline for symptomatic relief. Those who reported use of reliever medication on ≥ 5 of the last seventh days of the two-week run-in were randomized to one of the three following treatment groups for 24 weeks, bud/form maintenance and reliever therapy, fixed-dose bud/form or salm/flut. Patients were followed up after 8, 16, and 24 weeks of treatment (visits 3-5).

Efficacy measures

The primary efficacy outcome variable was the number of severe asthma exacerbations per patient over a six-month period. A severe exacerbation was defined as at least one of the following:

- Hospitalization/emergency room treatment due to asthma (patient initiated unscheduled healthcare visit due to asthma, leading to physician-initiated

additional asthma treatment at the visit)

- Oral glucocorticosteroid (GCS) treatment due to asthma for at least three days. If a patient had an exacerbation with a duration of >20 days that patient was discontinued from the study.

Cost estimation

The economic analysis was conducted from the perspective of the Thai healthcare providers. Medications included in the analysis included the study medication and the exacerbation-related use of oral steroids. The costs of study medications were calculated based on the medication use recorded in patient diaries. The number of days of oral steroid use was collected, and the average daily cost was calculated. Healthcare resource usage was composed of drugs, ambulance transports, intensive care, in-patient care, emergency room visits, visits to a specialist, visits to a primary care physician, other healthcare visits (nurse, physiotherapist), and home visits. Healthcare expenditures were estimated from the number of events reported in the case report form multiplied by the price per event. Additional medications were allowed during hospitalization or emergency room visits. As the unit cost of a hospitalization or an emergency room visit also incorporates medications used, this use was not calculated separately.

Other permitted medications included oral steroids for <20 days, mucolytics and expectorants not containing bronchodilators, antihistamines (other than terfenadine), and topical, nasal, and/or ocular formulations of glucocorticosteroids disodium cromoglycate and/or necromil sodium, and allergen specific immunotherapy if used for at least three months before visit 1 with the remainder of use occurring during the study. Medications considered necessary for the patient's safety and well-being were allowed at the discretion of the investigator.

For the estimation of budget impact analysis, we employed a 3% discount rate proposed by Edejer et al. [22].

Cost-effectiveness analysis

As a multi-national study, clinical effects were pooled, while the cost data used were those from Thailand [22]. Cost and exacerbation events were calculated as an average per patient over a six-month period. CE ratios comparing different treatment regimens were estimated for the patients in terms of

cost per exacerbation avoided. The incremental CE for the bud/form maintenance and reliever therapy relative to other treatment regimens was calculated as the ratio of differences (bud/form maintenance and reliever therapy minus other regimen) in costs and exacerbations avoided [23].

The bootstrap method [24] was employed to explore the variability for the estimates of CE. The joint distribution of costs and clinical outcomes was estimated from a study-sample of 2,000 replications. The results were presented in terms of confidence intervals (CI) of the incremental cost-effectiveness ratio (ICER) and CE plane.

Results

Three-thousand three hundred thirty five patients were randomized to study treatment. Data for 14 patients was excluded from the full analysis set. Then, 1107 were randomized to bud/form maintenance and reliever therapy, 1105 were randomized to bud/form, and 1123 were randomized to salm/flut. Out of these, 1052, 1046 and 1074 patients completed the study in the bud/form maintenance and reliever therapy, bud/form and salm/flut arms, respectively. The majority of patients randomized to each treatment arm completed the study. Eligibility criteria not fulfilled, adverse events, and lost to follow-up were the most common reasons for failure to complete the planned study period, and each event occurred at a similar rate across the three treatment arms.

Effectiveness

The analysis of severe exacerbations has been reported in the clinical study report by Kuna et al. [21], which is summarized in **Table 1**. Fewer patients

had at least one severe asthma exacerbation event in the bud/form maintenance and reliever therapy group (94 from 1103 cases or 8.5%) than in the salm/flut (12.3%) and bud/form (11.5%) groups. Patients in the bud/form maintenance and reliever therapy group experienced fewer severe exacerbations than those in the salm/flut and bud/form groups (125 vs. 208 and 173, respectively). The rate of severe exacerbations over the six-month observation period was 0.11 (11.3%; 125/1,103) in the bud/form maintenance and reliever therapy group, compared with 0.16 (15.7%; 173/1099) and 0.19 (18.6%; 208/1119) in the bud/form and salm/flut groups, respectively.

Resource use

Unit costs of medical services and drugs are shown in **Table 2**. A summary of the healthcare resources used is shown in **Table 3**.

Most resource use events were infrequent and similar among all treatment groups. The number of patients who were admitted to intensive care hospitalization from the bud/form maintenance and reliever therapy group was more than those from the bud/form and salm/flut groups (3 patients vs. 2 and 1 patient). In contrast to general care hospitalisation, the number of patients admitted in the bud/form maintenance and reliever therapy group was less than the other two groups (6 patients vs. 12 and 15 patients). Oral steroid use in the bud/form maintenance and reliever therapy group was about half the use in the other two groups with 1.89 days per six months vs. 3.18 and 3.36 days in the bud/form and salm/flut groups, respectively.

Table 1. Number of severe asthma exacerbations per treatment group for six months.

		Bud/form maintenance and reliever	Bud/form	Salm/flut
Patients (number)		1,103	1,099	1,119
Total time in study (days)		180,659	180,029	184,161
Severe asthma exacerbations	Number of patients with at least one event	94 (8.5%)	126 (11.5%)	138 (12.3%)
	Total number of events	125	173	208

Table 2. Unit cost of the resource used.

Health care contacts (unit)	Unit cost (TBT)	Reference
Ambulance transport (times)	1,200.00	Data from the central emergency medical services [23].
Hospitalisation, intensive care (days)	5,070.35	Mean divided by mean of LOS = 3.2. Data (2002-2003) adjusted by headline consumer price index from Bank of Thailand [17, 24].
Hospitalisation, general care (days)	1,953.71	Mean divided by mean of LOS = 3.2, Data (2002-2003) adjusted by headline consumer price index from Bank of Thailand [17, 24].
Emergency room visit (times)	483.80	Adjusted by CPI cost; includes doctor fee, laboratory and diagnostic fees [24, 25].
Visit to specialist (times)	250.00	Doctor fee [26].
Visit to primary health care physician (times)	100.00	Doctor fee [26].
Oral steroids (days)	3.00	Expert opinion: based on general practice around six tabs/week. Price = 0.50 TBT/tablet. exclude VAT [27].
Bud/form maintenance and reliever use (inhalations)	10.00	
Bud/form use (inhalations)	20.00	Twice compare with bud/form maintenance and reliever therapy, exclude VAT [27].
Salm/flut use (inhalations)	6.92	Salm/flut 25/125 pack size 120 doses, exclude VAT [28].
	14.93	Salm/flut 50/250 pack size 60 doses, exclude VAT [28].
Terbutaline use (inhalations)	1.80	Price list [27].

TBT=Thai Baht, LOS=length of stay, bud/form=budesonide/formoterol, salm/flut=salmeterol/fluticasone, VAT=value added tax.

A summary of the calculated six-month cost per patient when applying Thai unit costs to the healthcare resource use is also presented in **Table 3**. The cost of the study drugs was the highest in the bud/form group followed by the bud/form maintenance and reliever therapy group. The total direct cost per patient over six months was 5,745 Thai Baht (THB) in the bud/form maintenance and reliever therapy group, THB 7,882 in the bud/form group, and THB 5,760 in the salm/flut group.

Cost-effectiveness analysis

For all comparisons, bud/form maintenance and reliever therapy was the dominant treatment strategy with fewer exacerbations and a lower overall direct cost than other two comparator-regimens (**Table 4**). The study drug cost and total drug cost were lowest in the salm/flut group. The cost for resource use other than drug cost and the total direct cost were lowest in the bud/form maintenance and reliever therapy group.

Variability within the study sample is demonstrated in **Fig. 1**. The mean difference in costs between study groups is plotted against the mean difference in number of severe exacerbations for each of the 2,000 bootstrap replicates in the study population. The bootstrap analysis indicates that bud/form maintenance and reliever therapy remained dominant compared with bud/form (95%CI of the ICER: -549,434 and -22,376) and salm/flut (95%CI of the ICER: -4,634 and 7,169). The bootstrap analysis confirmed the comparison of bud/form maintenance and reliever therapy *vs.* bud/form. It also demonstrated that 95% of the re-sampling indicated bud/form maintenance and reliever therapy was superior over an ICER range of -549,434 to -22,376. In the case of bud/form maintenance and reliever therapy *vs.* salm/flut, the ICER indicated uncertainty for the point estimate since the 95% CI for the ICER: -4,634 and 7,169.

Table 3. Healthcare resource use and costs.

Variable	Treatment	Patients	Total events	Cost/ patient/ 6 months (THB)
Ambulance transport (times)	Bud/form maintenance + reliever	3	3	3.60
	Bud/form	4	7	8.40
	Salm/flut	7	11	13.20
Hospitalisation, intensive care (days)	Bud/form maintenance + reliever	3	24	121.69
	Bud/form	2	6	30.42
	Salm/flut	1	6	30.42
Hospitalisation, general care (days)	Bud/form maintenance + reliever	6	37	72.29
	Bud/form	12	94	185.60
	Salm/flut	15	149	289.15
Emergency room visit (times)	Bud/form maintenance + reliever	35	66	32.41
	Bud/form	33	60	29.51
	Salm/flut	49	90	43.06
Visit to specialist (times)	Bud/form maintenance + reliever	88	155	39.25
	Bud/form	98	192	48.75
	Salm/flut	113	206	51.00
Visit to primary healthcare physician (times)	Bud/form maintenance + reliever	71	139	14.10
	Bud/form	98	175	17.80
	Salm/flut	85	136	13.50
Total drug costs	Bud/form maintenance + reliever	1,100	n/a	5,461.89
	Bud/form	1,090	n/a	7,561.58
	Salm/flut	1,116	n/a	5,319.72
Other healthcare costs	Bud/form maintenance + reliever	n/a	n/a	283.34
	Bud/form	n/a	n/a	320.49
	Salm/flut	n/a	n/a	440.33
Total direct costs	Bud/form maintenance + reliever	n/a	n/a	5,745.23
	Bud/form	n/a	n/a	7,882.06
	Salm/flut	n/a	n/a	5,760.05

Bud/form=budesonide/formoterol, n/a=not applicable, salm/flut=salmeterol/fluticasone, THB=Thai Baht.

Table 4. Cost-effectiveness analysis.

	Bud/form maintenance + reliever	Bud/form	Salm/flut
Direct medical cost/patient/6 months (THB)	5,745.23	7,882.07	5,760.05
Events/patient/6 months	0.11	0.16	0.19
Incremental cost/ event avoided compared with bud/form maintenance + reliever	reference	dominated	dominated

Bud/form=budesonide/formoterol, salm/flut=salmeterol/fluticasone, THB=Thai Baht.

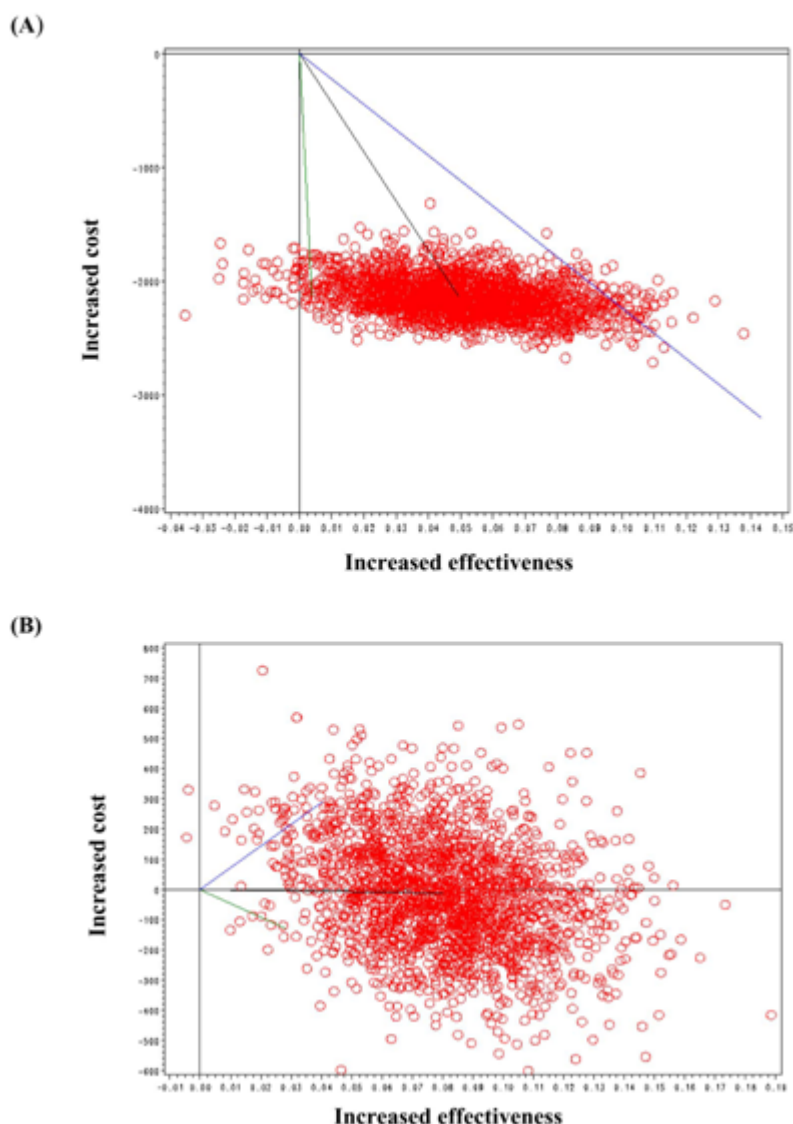


Fig. 1 Cost-effectiveness plane of bud/form maintenance and reliever therapy vs. fixed-dose bud/form (A) and bud/form maintenance and reliever therapy vs. salm/flut (B). Middle line indicates mean ICER, upper and lower lines indicate 95%CI of the ICER.

Discussion

The present results indicate that bud/form maintenance and reliever therapy is the dominant regimen compared with the bud/form and salm/flut regimens based on point estimates for the ICER. Compared with higher fixed-doses of bud/form and salm/flut, bud/form maintenance and reliever therapy reduced the incidence of severe exacerbations at a lower or similar overall. These results are consistent with the previous study by Price et al. [29].

The difference in treatment costs indicated, by extrapolation, that switching 1000 patients from fixed-dose bud/form to bud/form maintenance and reliever

therapy reduced the direct medical costs by more than two millions THB over a six-month period. Switching 1000 patients to bud/form maintenance and reliever therapy from salm/flut reduced costs by approximately 15,000 THB over a six-month period. The extrapolated savings to Thai healthcare was calculated based on the currently forecasted population [25], the prevalence of moderate and severe asthma in 6.8% of the adult population [26], and a 3% discount rate [22]. Interestingly, the present budget savings in patients over 18 years old during the forecasted period between the year 2007-2030 would be approximately 750 and 740 million THB for the high fertility

assumption and medium fertility assumptions, respectively.

In practice, salm/flut is offered in two fixed dose combinations, the salm/flut Evohaler® (25/125µg) and the salm/flut Accuhaler® (50/250 µg). These formulations are based on the assumption that the combination inhaler is at least as effective as its components administered separately [30], and assumes that two inhalations of the salm/flut Evohaler® is clinically equivalent to one inhalation of the salm/flut Accuhaler®. If prices of these two fixed-dose combinations are considered [31, 32], it is reasonable to conclude that bud/form maintenance and reliever therapy was superior to the salm/flut Accuhaler®.

In the current analysis, exacerbation data from the full clinical dataset was used to determine resource utilisation within the Thai healthcare system, and country specific unit costs were used to determine CE of the study drugs. Such approaches may be reasonable in determining country-specific CE data, because country-specific clinical studies are usually not practical given the cost of a large clinical study, and sub-analyses based on single country are not usually recommended, as there are few patients per country. In the absence of a sufficiently large country-specific datasets, pooling of data from individual countries is considered acceptable. Although there are techniques available for evaluating the appropriateness of such an approach [22], it remains a methodological challenge to pool data from various countries in a multi-national study for the purposes of CE analyses. In fact, relative prices of the component healthcare resources, utilization and reimbursement patterns, and patient behaviors are different within and between countries. Resourcing, cost, and indeed efficacy data derived for individual countries will not necessarily reflect that observed across a multi-national dataset or indeed that for other individual countries. Consequently, CE ratios and any cross-country comparisons based on analyses such as that described here should be viewed with caution.

The cost of medical services used in a study should be the national reference unit cost [27]. There is a limitation on such information in Thailand. For this reason, we used secondary cost data and acknowledge a difference in the level of quality of the data from various sources [28].

In conclusion, bud/form maintenance and reliever therapy was cost-effective and cost-saving compared with salm/flut and bud/form maintenance therapy

if applied in a Thai healthcare setting. Bud/form maintenance and reliever therapy reduced the number of severe asthma exacerbations leading to a reduction in the total direct medical costs compared with salm/flut and bud/form maintenance therapy.

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