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Published online: 27 Mar 2021.

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# Direct healthcare costs associated with management of asthma: comparison of two treatment regimens in Indonesia, Thailand and Vietnam

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**ABSTRACT**

**Objective:** Daily inhaled corticosteroid (ICS) and long-acting beta-2-agonist (LABA) combinations comprising either regular maintenance therapy with ICS/LABA plus as-needed short-acting beta-2-agonist (SABA) or ICS-formoterol combinations used as maintenance and reliever therapy (MART) are recommended for moderate asthma. This analysis compares the direct costs of twice-daily fluticasone propionate/salmeterol (FP/salm) and budesonide/formoterol MART in three Southeast Asian countries.

**Methods:** A literature review identified three randomized trials in patients with asthma (≥ 12 years) comparing regular twice-daily FP/salm with as-needed SABA versus MART in moderate asthma: AHEAD (NCT00242775/17 countries/2309 patients), COMPASS (AstraZeneca study SD-039-0735/16 countries/3335 patients), and COSMOS (AstraZeneca study SD-039-0691/16 countries/2143 patients). Economic analyses, conducted from a healthcare sector perspective (medication costs + healthcare utilization costs), applied unit costs from countries where healthcare costs are publicly available: Indonesia, Thailand and Vietnam. Results are expressed in British pound sterling (GBP/patient/year).

**Results:** Annual exacerbation rates were low and differences between treatment strategies were small (range, FP/salm: 0.31–0.38, MART: 0.24–0.25) although statistically significant in favor of MART. Total average (minimum-maximum) direct costs (in GBP/patient/year) across the three studies were £187 (£137–£284), £158 (£125–£190), and £151 (£141–£164) for those who used FP/salm, and £242 (£217–£267), £284 (£237–£340) and £266 (£224–£315) for MART in Indonesia, Thailand and Vietnam, respectively. On average, total direct costs/patient/year with FP/salm were 22.8%, 44.6% and 43.0% lower than with MART for Indonesia, Thailand and Vietnam, respectively.

**Conclusions:** In the three countries evaluated, total treatment costs with regular twice-daily FP/salm were consistently lower than with budesonide/formoterol MART due to lower direct healthcare costs.

## Introduction

The severity of a patient's asthma is based on the level of treatment required to control symptoms and to minimize the risk of exacerbations and, in this context, moderate asthma is defined as asthma that is well controlled with low dose daily inhaled corticosteroid (ICS) and long-acting beta-2-agonist (LABA) combinations comprising either regular maintenance therapy with ICS/LABA plus as-needed short-acting beta-2-agonist (SABA) as reliever therapy or ICS-formoterol combinations used as both maintenance and reliever therapy (MART) (1). Approximately 10–30% of patients with asthma are reported to experience exacerbations (2–4). Although poor asthma control and risk of exacerbation are related, they are not exactly concordant (5) and it is therefore important to assess both separately when considering treatment options.

In clinical practice, choice of treatment is based on evidence of efficacy and safety, cost, and individual patient factors (1). The efficacy and safety of regular maintenance therapy with the ICS/LABA combination fluticasone propionate/salmeterol (FP/salm) has been well-established in patients with moderate to severe asthma (6–15). MART treatment regimen with the combination of budesonide and formoterol has well-described efficacy in reducing the risk of severe exacerbations in studies of patients with moderate to severe asthma and a history of exacerbations (16,17).

In Southeast Asia, chronic respiratory disease is a leading cause of morbidity and mortality, imposing a huge economic burden (18). The cost of healthcare, including access to cost-effective medications, is an important aspect of tackling this burden (18). Previous studies comparing the costs of the FP/salm and MART regimens have mainly focused on

high-income countries in Europe (19–22), Canada (23) and Australia (21). To date, cost comparison data have been reported rarely for middle- or lower middle-income countries. A cost comparison in Thailand based on one head-to-head study reported slightly lower drug costs with the FP/salm compared with the MART regimen and similar overall direct costs (24).

The aim of this analysis was to compare the direct costs of FP/salm and MART in three Southeast Asian countries (Indonesia, Thailand and Vietnam) based on published data from three RCTs where the two treatments have been compared head-to-head (25–27). These countries were selected since the cost data for medications and health resources are publicly available. They may also be considered to be a representative sample of Southeast Asia in terms of population diversity, development and access to healthcare and medicines.

## Methods

### Clinical trials

A literature review was performed using Pubmed to identify RCTs comparing regular twice-daily FP/salm plus as needed SABA (hereafter referred to as FP/salm) versus budesonide/formoterol MART (hereafter referred to as MART) in adults and adolescents aged ≥12 years with asthma. Pubmed search terms included, "salmeterol/fluticasone"; "sal/flu"; "maintenance and reliever therapy"; "MART"; "randomized controlled trials"; "RCTs". Studies that recorded resource utilization data prospectively were identified, namely the AHEAD (NCT00242775 (25), COMPASS study (AstraZeneca study code SD-039-0735) (26) and COSMOS (AstraZeneca study code SD-039-0691) (27) trials. A summary of the study designs for each trial is shown in Table 1. AHEAD and COMPASS were double-blind, 6-month studies and COSMOS was an open-label 12-month study. The patient populations were similar across studies (mean baseline percent of predicted $FEV_1$ 71% to 73%). For this analysis, only data from the relevant FP/salm and MART treatment arms have been included.

### Resource utilization data

During all studies, the following resource use data were collected via patient notebooks or event logs: hospitalizations (intensive care and general ward), emergency room (ER) visits, and other healthcare visits including general practitioner (GP), specialist, physiotherapist and nurse (25–27). Scheduled study visits were excluded from the cost analyses. Medication use was either recorded in daily diaries and checked by the investigators at study visits (AHEAD and COMPASS) (25,26), or retrospective patient-reported medication use during the preceding 2 weeks recorded at clinic visits (COSMOS) (27). The dosing regimen for FP/salm and MART differed for the three studies in terms of medication inhalations per day as shown in Table 1. In addition, dose titrations were permitted in COSMOS but not in AHEAD or COMPASS.

Data concerning resource use were pooled across participating countries for each study and, for comparative purposes, data from the 6-month studies were extrapolated to 12 months - as reported previously (22).

### Economic analysis

Unit costs of branded medications and healthcare services in individual countries were obtained from publicly available sources (24,28–39) (Table 2). Where available, costs were based on the licensed dose (i.e. the dose approved in each country) and 60-dose (dry powder inhaler) or 120-dose (metered dose inhaler) packs, and were expressed as per dose/puff costs. In Thailand, terbutaline cost was not available so SABA costs were based on cost of salbutamol. In Vietnam,

**Table 1.** Study design of the three clinical studies.

|  | AHEAD[a] | COMPASS[b] | COSMOS[c] |
|---|---|---|---|
| **Study design** | 6-month, randomized, double-blind, parallel group | 6-month, randomized, double-blind, double dummy, parallel group | 12-month, randomized, open-label, parallel group |
| **Countries/sites** | 17/184 | 16/235 | 16/246 |
| **Treatment comparison** | FP/salm 500/50 μg x1 inhalation bid + terb as needed | FP/salm 125/25 μg x 2 inhalation bid + terb as needed | FP/salm 250/50 μg x1 inhalation bid (dose could be changed to 100/50 μg x1 inhalation bid or 500/50 μg x1 inhalation bid) + salb as needed |
|  | Bud/form 160/4.5 μg x2 inhalation bid + Bud/form as needed | Bud/form 320/9 μg x1 inhalation bid + terb as needed[d] | |
|  | | Bud/form 160/4.5 μg x1 inhalation bid + Bud/form as needed | Bud/form 160/4.5 μg x2 inhalations bid (dose could be changed to 160/4.5 μg x1 inhalations bid) + Bud/form as needed |
| **Number of randomized patients** | 2,309 | 3,335 | 2,143 |
| **Patient population** | | | |
| Mean age (years) | 39 | 38 | 45 |
| Mean baseline $FEV_1$ % predicted (%) | 71 | 73 | 73 |
| **Primary endpoint** | Time to first severe exacerbation | Time to first severe exacerbation | Time to first severe exacerbation |

*Note.* Bid: twice daily; Bud/form: budesonide/formoterol; FP/salm: fluticasone propionate/salmeterol; MART: maintenance and reliever therapy, salb: salbutamol; terb: terbutaline.
[a]Reference (25).
[b]Reference (26).
[c]Reference (27).
[d]Data from this study arm not included in economic analysis.

**Table 2.** Country specific unit costs (2019, conversion to British pound sterling (GBP)).

| Resource utilization measure | Indonesia | | Thailand | | Vietnam | |
|---|---|---|---|---|---|---|
| | Cost (rupiah) | Cost (GBP) | Cost (baht) | Cost (GBP) | Cost (dong) | Cost (GBP) |
| **Hospitalization, per day** | | | | | | |
| ICU | 17,363,900[a] | 961.56 | 5,070[b] | 127.93 | 2,100,000[c] | 71.38 |
| General ward | 8,628,000[a] | 477.79 | 1,953[b] | 49.28 | 1,156,230[c] | 39.30 |
| **Healthcare visit, per visit** | | | | | | |
| Emergency room | 1,198,100[a] | 66.35 | 796.36[d] | 20.09 | 1,267,750[e] | 43.09 |
| Specialist | 200,000[f] | 11.08 | 306[g] | 7.72 | 313,777[h] | 10.66 |
| General care physician | 80,000[f] | 4.43 | 101[g] | 2.55 | 355,321[h] | 12.08 |
| Other | 80,000[f] | 4.43 | 118[g] | 2.98 | 1,451,475[h] | 49.33 |
| **Home visit, per visit** | | | | | | |
| General care physician | 80,000[f] | 4.43 | 359.3[g] | 9.07 | 1,451,475[h] | 49.33 |
| Other | 80,000[f] | 4.43 | 359.3[g] | 9.07 | 1,451,475[h] | 49.33 |
| **Medication, per patient per dose/puff** | | | | | | |
| Bud/Form + Bud/Form (160/4.5 μg) | 2,238[i] | 0.12 | 7.42[j] | 0.19 | 5,001[k] | 0.17 |
| Bud/form (320/9 μg) | n/a | n/a | 10.52[j] | 0.27 | n/a | n/a |
| FP/salm (125/25 μg) | 1,155[l] | 0.07 | 2.50[j] | 0.06 | 1,972.98[k] | 0.07 |
| FP/salm (100/50 μg) | 1,817[i] | 0.10 | 6.42[j] | 0.16 | 3,945.96[l] | 0.07 |
| FP/salm (250/50 μg) | 2,042[i] | 0.11 | 7.79[j] | 0.20 | 4,524.80[k] | 0.15 |
| FP/salm (500/50 μg) | 2,233[i] | 0.12 | 9.95[j] | 0.25 | 5,865.40[k] | 0.20 |
| Salbutamol | 157[i] | 0.01 | 0.23[j] | 0.01 | 470.38[k] | 0.02 |
| Terbutaline (0.4 mg) | 622[i] | 0.03 | 0.23[j] | 0.01 | 470.38[k] | 0.02 |

*Notes.* Cost of FP/salm 100/50 (i.e. dry powder device) was not available, and per unit cost was assumed twice that of the FP/salm 125/25 (i.e. metered dose inhaler), since these are clinically equivalent. Bud/form: budesonide/formoterol; FP/salm: fluticasone propionate/salmeterol; ICU: intensive care unit.
Exchange rates used: 1 GBP = 18 058 rupiah; 1 GBP = 29 422 dong; 1 GBP = 39.63 baht (28).
[a]Reference (29).
[b]Reference (24).
[c]Reference (36).
[d]Reference (33).
[e]Reference (37).
[f]Reference (30).
[g]Reference (34).
[h]Reference (38).
[i]Reference (31).
[j]Reference (35).
[k]Reference (39).
[l]Reference (32).

FP/salm 100/50 (i.e. dry powder device) cost was not available, and per unit cost was assumed to be twice that of the FP/salm 125/25 (i.e. metered dose inhaler) unit cost, since these are clinically equivalent. Where the cost of health care visits for 'other health care personnel' (physiotherapist, occupational therapist or similar professional) was unavailable in the specific country, this was priced as the average cost of a GP visit and a visit to a physiotherapist.

Unit costs in local currency were converted to British pound sterling (GBP) using the 2019 average exchange rate (28). An expert in each country provided external validity of individual costings. Total direct costs (including medication and non-medication costs) per patient per year were calculated for each type of healthcare resource by multiplying the frequency of use over one year by unit costs for each country.

Several univariate sensitivity analyses were performed to test the robustness of the results in this analysis. The first sensitivity analysis, examined the impact on results of changing the unit cost of hospitalizations. In the main analyses, the differentiated unit cost at an intensive care unit and general ward was used. In the first sensitivity analysis, the average cost of ICU and general ward was used for hospitalization costs. In the second sensitivity analysis, the unit cost for a visit to a specialist was set equal to the unit cost for a GP visit. This was done to reflect clinical practice, where patients most often visit their GP with respect to their asthma. Finally, in the last two analyses, the unit costs for hospitalizations, health care visits and home visits were increased or decreased by 10%.

A sensitivity analysis was also performed by varying the health care unit costs by 10% or 20% to give estimated boundaries for the total costs.

## Results

### *Efficacy*

In the three comparator studies between FP/salm and MART selected because they could provide health economic data for this analysis, the primary endpoint, time to first severe exacerbation, was significantly prolonged in patients using MART compared with FP/salm in the COSMOS and

**Table 3.** Average resource use per patient per year by treatment option in each study.

| | AHEAD[a,b] | | COMPASS[b,c] | | COSMOS[b,d] | |
|---|---|---|---|---|---|---|
| | FP/Salm | MART | FP/Salm | MART | FP/Salm | MART |
| Hospitalization | | | | | | |
|   ICU | 0 | 0.01 | 0.012 | 0.048 | 0.005 | 0.009 |
|   General ward | 0.05 | 0.06 | 0.296 | 0.074 | 0.09 | 0.05 |
| Healthcare visit | | | | | | |
|   ED | 0.104 | 0.094 | 0.178 | 0.134 | 0.06 | 0.04 |
|   Specialist | 0.240 | 0.152 | 0.408 | 0.314 | 0.24 | 0.17 |
|   GP | 0.192 | 0.168 | 0.270 | 0.282 | 0.37 | 0.32 |
|   Other | 0.056 | 0.028 | 0.096 | 0.074 | 0.10 | 0.05 |
| Home visit | | | | | | |
|   GP | 0.016 | 0.010 | 0.016 | 0.006 | 0.04 | 0.03 |
|   Other | 0.006 | 0.002 | 0.044 | 0.006 | 0.01 | 0 |
| Medication (per patient per day) | | | | | | |
|   Bud/Form + Bud/Form (160/4.5 µg) | – | 4.879 | – | 3.250 | – | 3.940 |
|   Bud/form (320/9 µg) | – | – | – | – | – | – |
|   FP/salm (125/25 µg) | – | – | 4.304 | – | – | – |
|   FP/salm (100/50 µg) | – | – | – | – | 0.233 | – |
|   FP/salm (250/50 µg) | – | – | – | – | 1.214 | – |
|   FP/salm (500/50 µg) | 1.978 | – | – | – | 0.490 | – |
|   Salbutamol | – | – | – | – | 0.907 | – |
|   Terbutaline (0.4 mg) | 0.995 | – | 1.036 | – | – | – |

Notes. Data for AHEAD and COMPASS studies extrapolated to 1 year. Bud/form: budesonide/formoterol; ED: emergency department; FP/salm: fluticasone propionate/salmeterol; GP: general practitioner; ICU: intensive care unit.
[a]Reference (25).
[b]Resource use data from reference (24).
[c]Reference (26).
[d]Reference (27).

**Table 4.** Average total direct costs by treatment option in each study by country.

| Study | Country-treatment arm | Medication costs (GBP) | Healthcare costs (GBP) | Total direct costs (GBP) |
|---|---|---|---|---|
| AHEAD[a] | ID – FP/salm | 102 | 35 | 137 |
| | ID – MART | 220 | 47 | 267 |
| | TH – FP/salm | 183 | 7 | 190 |
| | TH – MART | 332 | 8 | 340 |
| | VT – FP/salm | 149 | 15 | 164 |
| | VT – MART | 302 | 13 | 315 |
| COMPASS[b] | ID – FP/salm | 113 | 171 | 284 |
| | ID – MART | 147 | 96 | 243 |
| | TH – FP/salm | 101 | 24 | 125 |
| | TH – MART | 221 | 16 | 237 |
| | VT – FP/salm | 111 | 35 | 146 |
| | VT – MART | 201 | 23 | 224 |
| COSMOS[c] | ID – FP/salm | 83 | 57 | 140 |
| | ID – MART | 178 | 39 | 217 |
| | TH – FP/salm | 147 | 10 | 157 |
| | TH – MART | 268 | 7 | 275 |
| | VT – FP/salm | 120 | 21 | 141 |
| | VT – MART | 244 | 14 | 258 |

Notes. Data rounded to nearest GBP. Bud/form: budesonide/formoterol; FP/salm: fluticasone propionate/salmeterol.
[a]Reference (25).
[b]Reference (26).
[c]Reference (27).

COMPASS studies (26,27) with no significant difference between treatments shown in the AHEAD study (25). The yearly exacerbation rate ranged from 0.24 to 0.25 for the MART and 0.31–0.38 for FP/salm treatment. Both treatments resulted in similar improvements in asthma control scores, asthma symptoms and lung function.
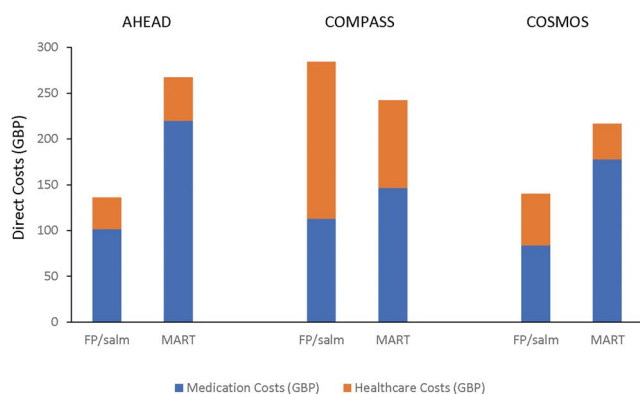
### Resource utilization data

Overall, healthcare resource use was relatively low in all three studies (Table 3). The most common healthcare use in all studies were visits to GPs and specialists and there were no notable differences between treatments in the frequency of these visits.
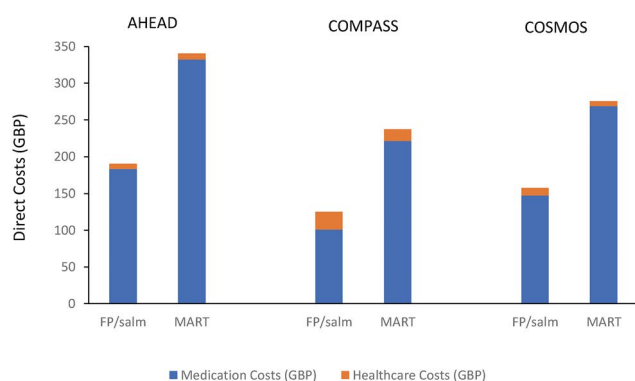
### Economic analysis

Average total direct costs per patient per year were consistently lower for those who used FP/salm compared with MART, with one exception (Indonesia/COMPASS study) (Table 4; Figure 1). Total average (minimum-maximum) direct costs (in GBP/patient/year) across the three studies
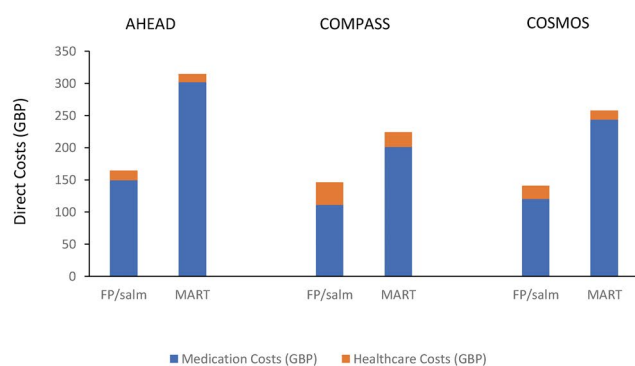
## a) Indonesia



## b) Thailand



## c) Vietnam



**Figure 1.** Average total direct costs by treatment option in each study in (a) Indonesia, (b) Thailand and (c) Vietnam.



**Figure 2.** Average total direct costs by treatment option across all studies in Indonesia, Thailand and Vietnam.

AHEAD study were slightly lower with FP/salm treatment versus MART.

The robustness of the presented analyses was tested by varying several parameters which could have impacted the unit costs of either hospitalizations or other healthcare visits. In each of the four sensitivity analyses conducted, the results of the analysis and conclusions remained unchanged.

## Discussion

The results of this analysis showed that, overall, regular twice-daily FP/salm was associated with lower direct healthcare costs compared with MART, despite the slightly higher exacerbation rates, and these findings were largely consistent across the three studies and the three countries evaluated. In general, healthcare resource use was low in all three studies, in keeping with the relatively low reported rates of severe exacerbations and accounting for the observation that differences in total direct costs were driven by the higher costs of MART than FP/salm treatment regimens.

Asthma-related costs impose a high burden on individual countries and costs differ between countries depending on several factors such as a country's gross domestic product (GDP), type of healthcare system and public health resources (40). Studies reporting the economic costs of the FP/salm and MART regimens in high-income countries, have shown less marked differences between treatments in terms of total direct costs, and no trend on one direction across studies, probably related to their different healthcare systems and drug pricing criteria (19–23). A previous analysis of cost data in Thailand based on the COMPASS study reported slightly lower drug costs with the FP/salm versus MART regimen and similar overall direct costs (24). Payers in Southeast Asian countries define cost thresholds or economic evaluation criteria relevant and specific to their healthcare system. In Indonesia, there is a single-payer, universal healthcare program called the National Health Insurance System (*Jaminan Kesehatan Nasional* – JKN) which provides cover for the majority of the population (41). In Thailand, universal healthcare is provided and reimbursed through three government schemes, and direct medical costs and specifically drug costs are an important consideration when prescribing medication. Vietnam has a

were £187 (£137–£284), £158 (£125–£190), and £151 (£141–£164) for those who used FP/salm, and £242 (£217–£267), £284 (£237–£340) and £266 (£224–£315) for MART in Indonesia, Thailand and Vietnam, respectively. On average, total costs per-patient per-year were 22.8%, 44.6% and 43.0% lower with FP/salm than MART for Indonesia, Thailand and Vietnam, respectively (Figure 2).

These differences were largely driven by the medication costs of each treatment regimen as in all countries the cost of MART treatment was higher than FP/salm treatment, whereas healthcare costs were generally higher with FP/salm versus MART treatment (Table 4). The exceptions to this were that healthcare costs in Indonesia and Thailand in the
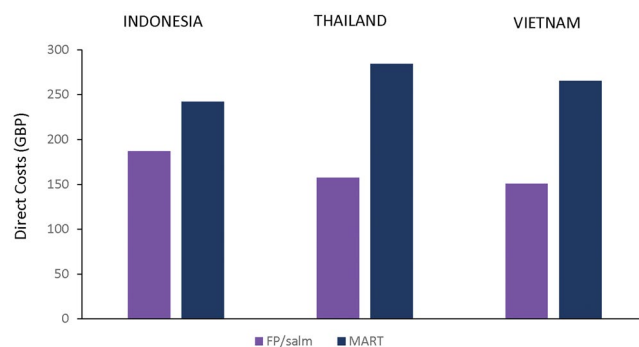
tiered health system and per patient visit cost thresholds are applicable within all medical care institutions other than the largest, regional central hospitals. In order to fall within thresholds, physicians may reduce the time between patient visits to reduce medication costs.

Our goal in this analysis was to reflect clinical practice, drug usage and costing; therefore, the real-world price of treatments in each country were used in our calculations. The difference in drug acquisition cost was a key driver of the overall cost presented per regime in this study, and these data will provide important information to decision makers. Both physicians and payers have to weigh up the overall evidence based on clinical data (efficacy, safety) and costs. In the three countries evaluated in this analysis, local asthma guidelines recommend both regular ICS/LABA and MART as preferred treatment options for moderate/severe asthma (42–44). In a recent survey of physicians in Asia, in addition to treatment guidelines and physician's personal experience, patient affordability of treatment was identified as an important factor influencing the choice of treatment by physicians for patients with asthma and co-existent rhinitis (45). Although hospitalizations due to asthma pose a significant cost, medications are the major contributor to overall costs of maintenance-treatment asthma management (1,46), since there are many patients with asthma but only a relative minority experience hospital admission (4,46). The data from our analysis showed that costs of medication was the most important driver of direct costs.

In the three studies that could be included in this analysis, differences in yearly exacerbation rates were very small but were significantly in favor of the MART strategy (25–27). Even in these studies where MART was associated with lower exacerbation rates, direct healthcare costs were lower with FP/salm. Across a range of clinical studies, superior benefit of MART is not consistently demonstrated (15,16,47–51). The cost advantage of FP/salm reported in this analysis, may therefore also apply more widely, dependent on local medication and treatment costs. In future research, inclusion of a budget impact analysis of different treatment regimens for asthma with country specific epidemiological data, or factoring asthma control into healthcare cost computations would be of added interest.

A main limitation of this analysis is that we could not include indirect costs associated with asthma, such as absenteeism, because of difficulties in obtaining consistent estimates of unit costs in the countries included in this analysis; instead we focused on direct costs associated with healthcare resource use and medication costs. Even though the countries included in this analysis were similar in terms of populations, development and access to healthcare, the costing data with these three countries in Southeast Asia may not be representative more extensively. However, our analysis prepares the way for future such research. While the majority of unit costs data were obtained from publicly available, verifiable resources, we were required to make a limited number of assumptions about individual unit costings where a particular drug or drug formulation was not available in a particular country. However, these were rational assumptions based on clinically equivalent alternatives, and were validated with a local expert in the relevant country, as is a standard practice for these types of healthcare cost studies. A further criticism may be the lack of inclusion of recent clinical trials; all of those included here were undertaken over a decade ago, although the approach in clinical practice and treatment guideline recommendations for moderate asthma are largely the same (1,51). Another limitation is that resource use data were based on clinical trials only, using data collected in notebooks or event logs, although this is commonly used in cost-effectiveness analyses and reported to have high internal validity (22). The same resource use data have been used and reported in several other cost analyses publications based on these studies (19–24). With respect to external validity, the three countries included in this analysis participated in the AHEAD study, Thailand and Vietnam participated in the COMPASS study, and Vietnam participated in the COSMOS study. The external validity of these data was also provided by advice taken from experts in each country. While the use of clinical trials data was helpful at standardizing data collection across multiple geographies, further data collection should be done to measure the real-world impact of different treatment approaches in asthma.

## Conclusion

This study showed that, overall, treatment with regular twice-daily FP/salm is associated with lower direct healthcare costs than budesonide/formoterol MART. This difference was consistent across the three countries evaluated. These data provide important information for both physicians and payers with respect to treatment decisions for patients with moderate asthma in Indonesia, Thailand and Vietnam.

## Declaration of interest

BA, PWJ, AI and SA are employees of GSK and hold GSK stocks/shares. WB has received personal fees from AstraZeneca Thailand, Boehringer Ingelheim and Thai Otsuka. FY and LTTL report no conflicts of interest.

## Availability of data and materials

Information on GSK's data sharing commitments and requesting access can be found at: https://www.clinicalstudydatarequest.com.

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