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ORIGINAL RESEARCH ARTICLE

Cost-effectiveness analysis of budesonide/formoterol (Symbicort®) as needed for mild asthma in Malaysia

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Abstract

Background Budesonide/formoterol (Symbicort®) as needed (PRN) is effective for the prevention of severe exacerbations in mild asthma.

Objective This economic model evaluated the cost effectiveness of budesonide/formoterol PRN versus (1) a short-acting β_2-agonist (SABA) PRN and (2) maintenance budesonide plus SABA PRN for mild asthma in Malaysia.

Methods A decision analytical model was developed to evaluate the downstream economic consequences of the comparators from the payer's perspective (i.e. Ministry of Health, Malaysia) with a fixed time horizon of 1 year, and no discounting was applied. Data were derived from published clinical trials (i.e. SYGMA 1, SYGMA 2, and Novel START), the latest Malaysian resources, and an expert panel. The incremental cost-effectiveness ratio (ICER) per severe exacerbation avoided was determined. Sensitivity and scenario analyses were conducted to examine the robustness of the model.

Results Treatment with budesonide/formoterol PRN (Malaysian ringgit [RM]773.39) had a lower total annual cost than SABA PRN (RM908.27) but a slightly higher cost than maintenance budesonide (RM760.51). The main cost driver was the disease management cost. Budesonide/formoterol PRN was a dominant intervention compared with SABA PRN and was associated with an ICER of RM696.11 per severe exacerbation avoided compared with maintenance budesonide. Scenario analysis with data from the Novel START trial indicated that budesonide/formoterol PRN was a dominant intervention compared with both SABA PRN and maintenance budesonide. Model outcomes were most affected by the mean inhalation of budesonide/formoterol PRN, the cost of managing severe exacerbations in hospital, and the probability of severe exacerbations with maintenance budesonide.

Conclusion From the Malaysian healthcare payer perspective, budesonide/formoterol PRN is either a dominant or likely to be a cost-effective treatment option in managing mild asthma.

Introduction

Asthma is a common chronic disease that presents with respiratory symptoms, limitation of activity, and exacerbations that may require urgent hospital treatment and can be fatal [1]. Its global prevalence varies widely across countries, with Australia having the highest rate, at 21.5% [2]. The *Third National Health and Morbidity Survey 2006* reported that 4.5% of the adult Malaysian population have asthma [3]. Alarmingly, asthma cases increase tremendously, by 50%, every 10 years [4], resulting in substantial healthcare costs, in addition to causing loss of productivity, poor quality of life, disability, and even death.

The fundamental pathogenesis of asthma exacerbation is airway inflammation driven by various environmental factors. Acute airway inflammation leads to airway smooth muscle constriction (bronchospasm) and hypersecretion of mucus and oedema [5], causing reversible airway narrowing and increased airway resistance. The associated symptoms are usually temporarily relieved with a β_2-agonist. However, superimposed acute and subacute inflammatory episodes because of inadequate anti-inflammatory treatment lead to an aberrant injury–repair mechanism and remodelling of the airway wall. Ultimately, this results in airway wall thickening and a varying degree of fixed airflow obstruction with decreased lung function [5]. Accordingly, one of the primary

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Key Points

Budesonide/formoterol as needed (PRN) is reported to be effective in the prevention of severe exacerbations in mild asthma; however, limited cost-effectiveness data are available to facilitate informed decision making among healthcare policy makers.

The findings of this study revealed that budesonide/formoterol PRN is either a dominant or likely to be a cost-effective treatment option in managing mild asthma from the Malaysian healthcare payer perspective.

aims of asthma management, as highlighted in international guidelines, is to minimise the future risk of exacerbations (inflammatory episodes) via adequate use of inhaled corticosteroid (ICS)-containing controller medication [1, 6].

The regimen for corticosteroid usage is stratified according to asthma severity. The severity of asthma can be classified as mild, moderate, or severe according to the level of treatment required to control symptoms and exacerbations [1]. Mild asthma is well-controlled with step 1 or step 2 treatment [1] and is estimated to affect between 50% and 75% of all patients with asthma [7]. A recent Malaysian study showed that 81% of patients with asthma had mild asthma, and 50% were inadequately controlled [8]. More importantly, patients with mild asthma contributed 30–40% of all asthma exacerbations that required emergency management [7], justifying the current efforts for re-strategising treatments for patients with mild asthma.

Healthcare professionals and patients with mild asthma commonly perceive the risk of maintenance ICS treatment to outweigh its benefits because of the relatively milder symptoms. This causes over-usage and reliance on short-acting β_2-agonists (SABAs) for symptom control and leads to a higher risk of exacerbations [9]. Taking advantage of patients' natural relief-seeking behaviour when symptomatic, symptom-driven use of a combination of an ICS and a fast-onset long-acting β_2-agonist was investigated. In this context, two randomised, double-blind, placebo-controlled clinical trials (SYGMA 1 and 2) showed that the use of budesonide/formoterol (Symbicort®) as needed (PRN) (symptom driven) in mild asthma was non-inferior in preventing the risk of severe exacerbation and required only 17–25% of the median daily dose of glucocorticoid compared with maintenance budesonide plus SABA PRN therapy [10, 11]. These findings have been extended to pragmatic, open-label clinical trials to better reflect clinical practice and treatment effectiveness [12, 13].

Despite the promising treatment outcomes of budesonide/formoterol PRN in mild asthma, its economic impact remains relatively unexplored. Therefore, this economic model aimed to evaluate the cost effectiveness of using budesonide/formoterol PRN versus (1) SABA PRN and (2) maintenance budesonide plus SABA PRN in patients with mild asthma in Malaysia. Recognising that compliance with maintenance ICS for patients with mild asthma is critical to the outcomes of the treatment regimens, the current model also aimed to determine the cost effectiveness of budesonide/formoterol PRN versus these two comparators to further enhance its external validity.

Methods

This article was written in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [14].

Patient population

The patient population was from the SYGMA 1 trial [10], were aged ≥ 12 years, and had mild asthma needing Global Initiative for Asthma (GINA) step 2 treatment. The patients had either (1) uncontrolled asthma symptoms while taking inhaled short-acting bronchodilators PRN or (2) well-controlled asthma on maintenance therapy with a low-dose ICS or leukotriene-receptor antagonist plus short-acting bronchodilators PRN. Scenario analysis involved the adult patient population from the Novel START trial [12] with milder symptoms requiring short-acting bronchodilators PRN as the sole asthma therapy.

Model comparators

The comparators for this economic evaluation were as follows:

- Budesonide/formoterol 160/4.5 µg PRN (budesonide/formoterol PRN group)
- Salbutamol 100 µg PRN (SABA PRN group)
- Maintenance budesonide 200 µg twice daily + salbutamol 100 µg PRN (maintenance budesonide group).

Model structure

A decision analytical model (Fig. 1) was constructed to depict the downstream economic consequences of using the aforementioned comparators for patients with mild asthma treated at Ministry of Health (MOH) facilities, Malaysia. Upon receiving treatment, a patient would either have no severe exacerbation or experience severe exacerbation. Severe exacerbation was selected as the effectiveness variable [15] for the current model and was defined as worsening

asthma condition requiring emergency department management, inpatient hospitalisation, or the use of systemic glucocorticoids for at least 3 days [10, 11].

Perspective and time horizon

The Malaysian healthcare system is characterised by a two-tier system of public and private healthcare sectors. The public healthcare sector system is funded by the government and the MOH, as the largest healthcare service provider in Malaysia. Accordingly, this economic evaluation was conducted from the payer's perspective (i.e. MOH Malaysia). A fixed time horizon of 1 year was used in the model, so no discounting was applied to costs or outcomes.

Model inputs

Cost data

All costs were expressed in 2020 Malaysian ringgit (RM). Given the payer's perspective, only direct medical costs were included in the analysis (e.g. drug acquisition costs, costs associated with management of severe exacerbations at an emergency department or inpatient hospitalisation, and costs of scheduled clinic visits). Cost inputs were obtained from the latest Malaysian resources. All drug costs were obtained from IMS price information and the manufacturer. Disease management costs for patients with severe exacerbations included the costs of managing acute exacerbations at an emergency department or as an inpatient and the costs of clinic visits for disease monitoring. Patients with severe exacerbations would have more frequent clinic visits over a 1-year duration, as indicated by the expert panel. On the other hand, for patients with no severe exacerbations, only the costs of clinic visits for disease monitoring were included as disease management costs. These direct medical cost data were obtained from a published Malaysian study [16] and were adjusted according to the Malaysian consumer price index [17]. All cost input variables and data sources are presented in Table 1.

The current model did not include separate adverse event (AE) management costs. This is because all treatment comparators had similar AE profiles, except for the percentage of patients with AEs that led to discontinuation [10]. These AEs consisted of two components. First, the non-specified AEs that were not detailed in the SYGMA 1 trial posed challenges when estimating the costs of managing these AEs, so they were not incorporated into the model. These non-specified AEs also involved only six patients in the budesonide/formoterol PRN group, 16 in the SABA PRN group, and nine patients in the maintenance budesonide group so would have had a negligible impact on the model outcome. The second component was AEs that led to asthma-related discontinuation, defined as (1) a severe asthma exacerbation with a duration > 3 weeks, (2) two severe asthma exacerbations in 3 months, or (3) three severe asthma exacerbations during the study. The outcomes of these asthma-related discontinuations (i.e. the number of severe exacerbations) were incorporated in the trial analysis to determine the annualised severe exacerbation rate across the comparator groups [10]. Therefore, the costs of managing AEs that led to asthma-related discontinuations were not included in the current model to avoid double counting.

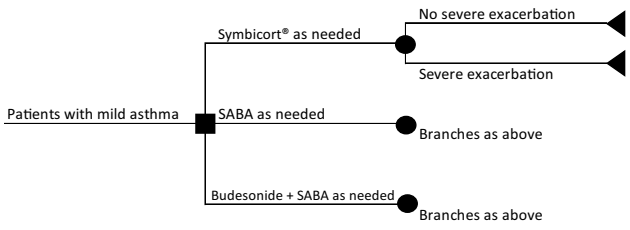

Fig. 1 Decision analytical model for mild asthma. *SABA* short-acting β_2-agonist

Dosing regimen and efficacy data

The mean inhalations of budesonide/formoterol (0.52 ± 0.55) and SABA (0.49 ± 0.70) administered PRN per day in the maintenance budesonide group were derived from the SYGMA 2 trial. Because of the lack of published data, the mean inhalation of SABA administered per day in the SABA PRN group was assumed to be the same as those of SABA administered per day in the maintenance budesonide group. The efficacy data (e.g. the annualised severe exacerbation rate) were obtained from the SYGMA 1 trial. These data were used to derive the outcome probabilities (i.e. the probability of severe exacerbation) for all three comparators.

Additional data provided by the expert panel

An expert panel was consulted to provide data relevant to the local setting but not available from the published literature. The expert panel comprised 12 chest consultants and two family physicians with extensive experience in managing patients with asthma in Malaysia. The panel determined that the dosing regimens used in the current model were generalisable to the Malaysian setting. The expert panel estimated that 80% of patients with severe exacerbations would require hospitalisation and another 20% would be adequately managed in an emergency department. Patients with good symptom control and no severe exacerbations would have an average of three clinic visits a year for disease monitoring. In contrast, those who experienced severe exacerbations would be followed up in the clinic an average of six times per year. The expert panel also agreed that the efficacy of salbutamol

Table 1 Input parameters for the model, including ranges and distribution

Variables	Base-case value	Range for DSA	Distribution for PSA	References
Probability of severe exacerbation				
Budesonide/formoterol PRN	0.0676 *0.0409*	0.0541–0.0811 *0.0327–0.0491*	Beta	SYGMA 1 [10] Novel START [12]
SABA PRN	0.1813 *0.1031*	0.1450–0.2176 *0.0825–0.1238*	Beta	
Maintenance budesonide	0.0861 *0.0933*	0.0689–0.1033 *0.0747–0.1120*	Beta	
Mean inhalations administered per day				
Salbutamol PRN (in SABA PRN group)	0.49[a] *1.01*	0.00–1.19 *0.00–2.61*	Gamma	SYGMA 2 [11] Novel START [12]
Budesonide/formoterol PRN	0.52 *0.53*	0.00–1.07 *0.00–1.07*	Gamma	
Salbutamol PRN (in maintenance budesonide group)	0.49 *0.52*	0.00–1.19 *0.00–1.55*	Gamma	
Budesonide	2.00[b] *1.11*	1.60–2.00 *0.55–1.67*	Gamma	
Costs				
Clinic visit	172.90	136.55–209.25	Gamma	Yong and Shafie [16] and cost were adjusted to the year 2020 RM
Severe exacerbation managed in the ED	48.58	40.64–56.52	Gamma	
Severe exacerbation managed as inpatient (hospitalisation)	1987.25	895.21–3079.29	Gamma	
Drug acquisition for budesonide/formoterol	70.50	56.40–84.60	Gamma	AstraZeneca
Drug acquisition for salbutamol	6.20	4.96–7.44	Gamma	IMS average pack price
Drug acquisition cost for budesonide	22.15	17.72–26.58	Gamma	
Proportion of patients with severe exacerbation treated in the ED	20%	16–24%	Beta	Expert panel
Mean frequency of clinic visit				
If no severe exacerbation	3.00	2.00–4.00	Gamma	
If severe exacerbation	6.00	3.00–9.00	Gamma	

Costs are presented in RM. When two different base-case values are shown for a single input parameter, the one in *italics* was obtained from the Novel START trial and was used for scenario analysis. The input parameters with a single base-case value were used in both the main and the scenario analyses

DSA deterministic sensitivity analysis, *ED* emergency department, *PRN* as needed, *PSA* probabilistic sensitivity analysis, *RM* Malaysian ringgit, *SABA* short-acting β_2-agonist

[a]The mean inhalation of SABA administered per day in the SABA PRN group was assumed to be the same as the mean inhalation of SABA administered per day in the maintenance budesonide group

[b]The mean inhalation of budesonide administered was assumed as two per day

as a reliever therapy is similar to that of terbutaline, as demonstrated in several studies [18–20].

Model assumptions

The current model included the following assumptions.

- The mean inhalation of SABA administered per day in the SABA PRN group was assumed to be the same as those of SABA administered per day in the maintenance budesonide group.
- The mean inhalation of maintenance budesonide administered was assumed to be two per day.
- The choice of inhaler chosen for the calculation was based on the highest usage within each drug class as reported by the IMS analysis manager (Malaysia).
- The efficacy of salbutamol, the primary SABA used in the Malaysian setting, as a reliever therapy was assumed to be similar to that of terbutaline [18–20].
- Each patient with severe exacerbations was assumed to experience an episode of severe exacerbation in a year.
- In total, 80% of patients with severe exacerbations were assumed to be treated as inpatients (hospitalisation) and 20% adequately managed at an emergency department.
- We assumed no differences in costs for managing other AEs that did not lead to discontinuation given that the

rate of these AEs was similar across all comparators [10], so this cost was not populated in the current model.

Cost calculation and model outcome

Cost calculation

The cost per patient without severe exacerbations was calculated as the sum of the drug acquisition cost of each comparator and the costs of clinic visits for disease monitoring over 1 year. The cost per patient with severe exacerbation included the drug acquisition cost, the costs of managing acute exacerbation at an emergency department or hospitalisation, and the costs of clinic visits for disease monitoring over 1 year.

Incremental cost-effectiveness ratio

In cost-effectiveness analysis (CEA), an incremental cost-effectiveness ratio (ICER) is used in making an informed decision about interventions that are more costly but more effective than comparators [21]. The incremental cost per severe exacerbation avoided was determined for the comparator in the current model. An intervention is considered a dominant treatment option if it is cheaper and more effective than the comparator.

Sensitivity analysis

Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted to evaluate the robustness of the model's outcomes by modifying the model's variables within plausible ranges from the base-case values. These included changes in key variables (i.e. drug acquisition costs; mean inhalation of budesonide/formoterol PRN, SABA PRN, or maintenance budesonide administered per day; probability of severe exacerbations; costs of disease management) and the expert panel's estimates (i.e. mean frequency of clinic visit for those with or without severe exacerbations, percentage of patients with severe exacerbations managed in the emergency department). For the variables with no published standard error or confidence intervals, input with a ± 20% from the base-case values was explored. The mean inhalation per day for maintenance budesonide was set at the upper limit of two (the prescribed regimen) and tested at a plausible lower limit (i.e. − 20%) (Table 1). The input variables that had the most influence on the model's outcomes were determined and presented in tornado diagrams.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed with a Monte Carlo simulation of 10,000 iterations using TreeAge Pro® (TreeAge Software Inc., MA, USA). Input variables (i.e. probability of severe exacerbations, percentage of patients with severe exacerbations managed in the emergency department) were allowed to vary simultaneously according to a beta distribution, with an uncertainty of ± 20% from the base-case value. On the other hand, cost inputs (i.e. costs associated with the management of severe exacerbations, costs of clinic visits, and drug acquisition costs); mean inhalations of budesonide/formoterol PRN, SABA PRN, or maintenance budesonide administered per day; and mean frequency of clinic visits for those with or without severe exacerbations were assigned to a gamma distribution (Table 1). A cost-effectiveness acceptability curve was constructed to estimate the probability of budesonide/formoterol PRN as a cost-effective option in treating patients with mild asthma compared with the other two alternatives.

Scenario analysis

Given the poor compliance with maintenance budesonide therapy and the impact of that on its effectiveness in preventing severe exacerbations in patients with mild asthma, an exploratory scenario analysis was performed to assess the cost effectiveness of budesonide/formoterol PRN compared with the aforementioned comparators using data inputs from the Novel START trial [12]. The model inputs were essentially the same except that the probability of severe exacerbations and the mean inhalations of budesonide/formoterol PRN, SABA PRN, and maintenance budesonide administered per day were obtained from the Novel START trial [12]. As with the SYGMA trials, in the Novel START trial [12], all treatment comparators were reported to have similar AE profiles; therefore, the cost of managing AEs was not included. Sensitivity and scenario analyses were conducted using the range of input parameters, as presented in Table 1, to determine the robustness of the model's outcomes.

Results

Base-case analysis

The main cost driver for all comparators was the disease management costs (i.e. the costs associated with clinic visits for disease monitoring and the management of severe exacerbations), which accounted for 95.9–99.8% of the total annual cost for patients with severe exacerbations (Table 2). The same observation was also noted among those with no severe exacerbations, in which the disease management cost

(i.e. the cost of clinic visits for disease monitoring) contributed to 82.3–98.9% of the total annual cost (Table 2).

As shown in Table 3, treatment with budesonide/formoterol PRN (RM773.39) was associated with a reduced total annual cost of RM134.88 when compared with SABA PRN (RM908.27). On the other hand, treatment with budesonide/formoterol PRN incurred a small incremental cost of only RM12.88 annually over maintenance budesonide (RM760.51) (Table 3). Treatment with budesonide/formoterol PRN was associated with fewer severe exacerbations than both comparators (i.e. SABA PRN and maintenance budesonide). As such, treatment with budesonide/formoterol PRN was a dominant intervention (i.e. more effective and cheaper) over SABA PRN and was associated with an ICER of RM696.11 per severe exacerbation avoided when compared with maintenance budesonide.

One-way sensitivity analysis

In the model comparing budesonide/formoterol PRN versus SABA PRN, one-way deterministic sensitivity analysis showed the two factors that most affected the model's outcomes (i.e. incremental costs) were (1) the mean inhalation of budesonide/formoterol PRN administered per day and (2) the cost of managing severe exacerbations in the hospital setting (Fig. 2a). On the other hand, when comparing budesonide/formoterol PRN versus maintenance budesonide, the probability of severe exacerbations in the maintenance budesonide group had the most influence on the model's outcomes (i.e. ICER per severe exacerbation avoided), followed by the mean inhalation of budesonide/formoterol PRN administered per day (Fig. 2b). The cost of managing severe exacerbations in the emergency department had the least impact on both model outcomes. Figure 2 presents the tornado diagrams for budesonide/formoterol PRN versus SABA PRN and for budesonide/formoterol PRN versus maintenance budesonide.

Probabilistic sensitivity analysis

Based on the Monte Carlo simulation of 10,000 iterations, the mean total annual cost of budesonide/formoterol PRN was RM775.40 (95% confidence interval [CI] 383.86–1332.54). The SABA PRN group attained a higher mean total annual cost (RM911.42; 95% CI 464.74–1527.30), whereas the maintenance budesonide group incurred a lower mean total cost (RM762.94; 95% CI 409.70–1272.38). Given the lower mean severe exacerbation events in the budesonide/formoterol PRN group, treatment with budesonide/formoterol PRN was a dominant intervention (i.e. more effective and cheaper) compared with SABA PRN. The probability of budesonide/formoterol PRN being a cost-effective option for patients with mild asthma compared with the comparators is shown in Fig. 3.

Table 2 Cost component of mild asthma treatment for each comparator

Comparator	Drug cost	Disease management cost		Total cost	
		With no severe exacerbation	With severe exacerbation	With no severe exacerbation	With severe exacerbation
Budesonide/formoterol PRN	111.51	518.69	2636.90	630.20	2748.41
SABA PRN	5.54	518.69	2636.90	524.24	2642.45
Budesonide BID + SABA PRN	59.44	518.69	2636.90	578.14	2696.34

Costs are presented as Malaysian ringgit. Input variables were obtained from SYGMA trials (main analysis)

BID twice daily, *PRN* as needed, *SABA* short-acting β_2 agonist

Table 3 Proportional cost of each comparator

Comparator	Without severe exacerbation			With severe exacerbation			Total cost
	Probability	Cost	Proportional cost	Probability	Cost	Proportional cost	
Budesonide/formoterol PRN	0.9324	630.20	587.60	0.0676	2748.41	185.79	773.39
SABA PRN	0.8187	524.24	429.19	0.1813	2642.45	479.08	908.27
Budesonide BID + SABA PRN	0.9139	578.14	528.36	0.0861	2696.34	232.16	760.51

Costs are presented as Malaysian ringgit. Input variables were obtained from SYGMA trials (main analysis)

BID twice daily, *PRN* as needed, *SABA* short-acting β_2-agonist

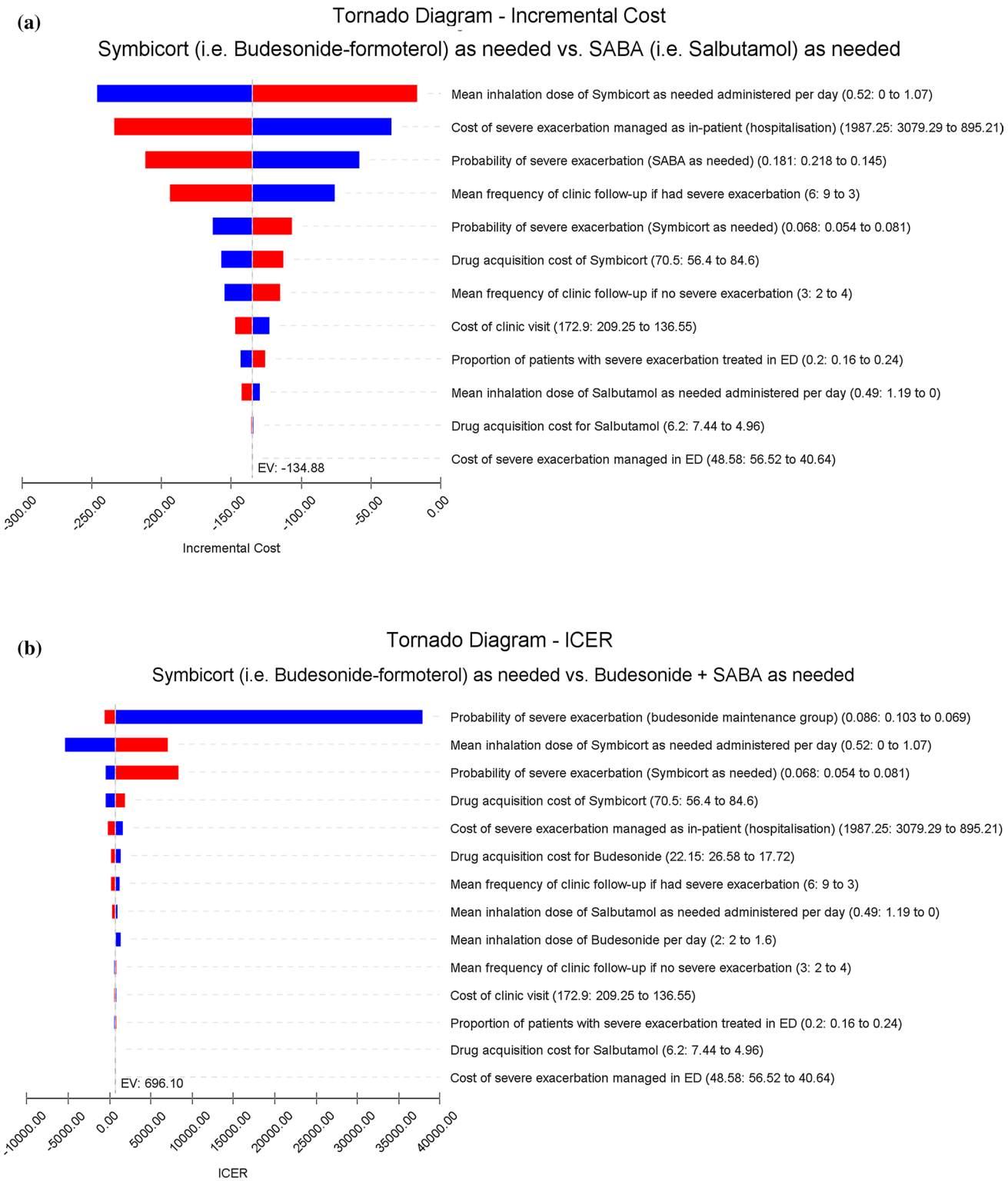

Fig. 2 Tornado diagram for Symbicort® PRN versus **a** SABA PRN and **b** budesonide BD + SABA PRN. *BID* twice daily, *ED* emergency department, *ICER* incremental cost-effectiveness ratio, *PRN* as needed, *SABA* short-acting β_2-agonist

Scenario analysis

When the model was populated with data from the Novel START trial, budesonide/formoterol PRN was a dominant intervention compared with either SABA PRN or maintenance budesonide. Treatment with budesonide/formoterol PRN (RM719.00) was associated with a lower total annual cost of RM29.59 and RM33.19 when compared with SABA PRN (RM748.59) and maintenance budesonide (RM752.19), respectively. In addition, treatment with budesonide/formoterol PRN was associated with fewer severe exacerbations when compared with SABA PRN and maintenance budesonide. The disease management costs remained the main cost driver for all comparators, accounting for 95.9–99.6% and 82.0–97.8% of the total annual cost for those with and without severe exacerbations, respectively.

As illustrated in the tornado diagrams, the mean inhalation of budesonide/formoterol PRN administered per day and the cost of managing severe exacerbations in the hospital (Fig. 4a, b) were the two factors most affected the model's outcomes (i.e. incremental cost). Similarly, the cost of managing severe exacerbations in the emergency department had the least impact on both model outcomes.

Probability sensitivity analysis showed that the mean total annual cost of budesonide/formoterol PRN was RM721.14 (95% CI 348.37–1270.40). Both SABA PRN and maintenance budesonide incurred higher mean total annual costs (RM751.25 [95% CI 382.12–1279.70] and RM754.77 [95% CI 394.20–1273.34], respectively). The probability of budesonide/formoterol PRN being a cost-effective option for patients with mild asthma compared with the comparators is shown in Fig. 5.

Discussion

This is the first CEA to indicate that budesonide/formoterol PRN is a dominant (vs. SABA PRN) and likely to be a cost-effective (vs. maintenance budesonide) option for patients with mild asthma in the Malaysian setting.

Although patients with mild asthma have relatively infrequent and less bothersome symptoms, this group of patients are known to be at risk of serious adverse outcomes, including exacerbation-related hospitalisation and death [7]. Studies have shown that 16% of patients with near-fatal asthma and 20% of adults dying of asthma were considered to have mild asthma [7]. In fact, patients with mild asthma are reported to have an average frequency of 0.12–0.77 severe exacerbation attacks per year [7]. Severe exacerbations in patients with mild asthma contribute to 30–40% of all asthmatic exacerbations treated at the emergency department [22, 23].

Inhaled SABA PRN has been the longstanding first-line treatment for mild asthma over the past five decades, when asthma was once thought to be primarily a disease of bronchoconstriction. Previous GINA guideline stated that patients with mild asthma can be well-managed with either reliever alone (i.e. SABA PRN alone) or with the additional use of controllers (i.e. low-dose ICS) [24]. Given the rapid relief of symptoms using relievers, patients with mild asthma are generally over-reliant on SABA PRN treatment and are not satisfied with or adherent to controller medications for which effects are not immediately perceivable. Furthermore, the high effectiveness of SABA used in managing asthma exacerbations at the emergency department and hospital settings, the easy accessibility of SABA as a non-prescription

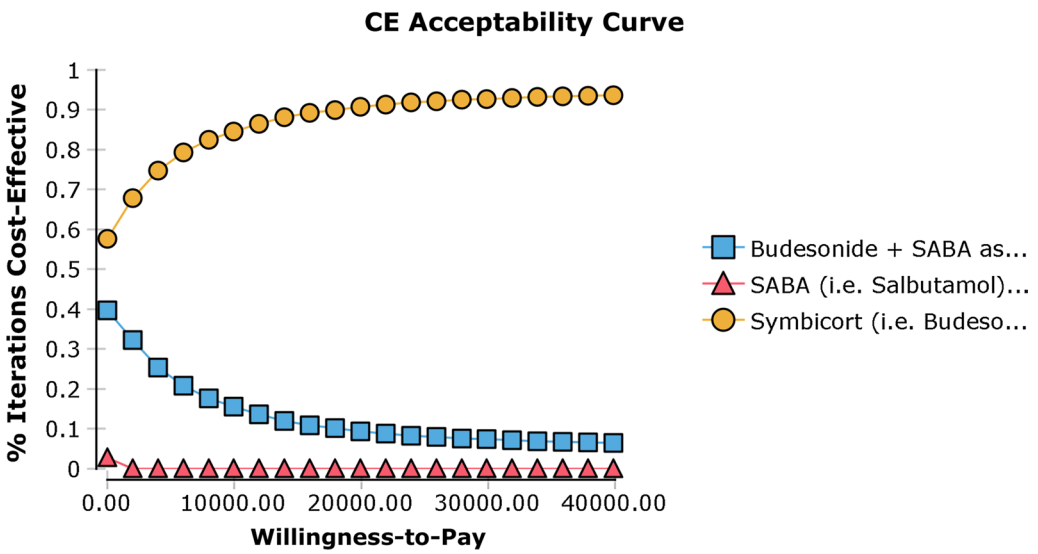

Fig. 3 Cost-effectiveness acceptability curve. *CE* cost effectiveness, *SABA* short-acting β_2-agonist

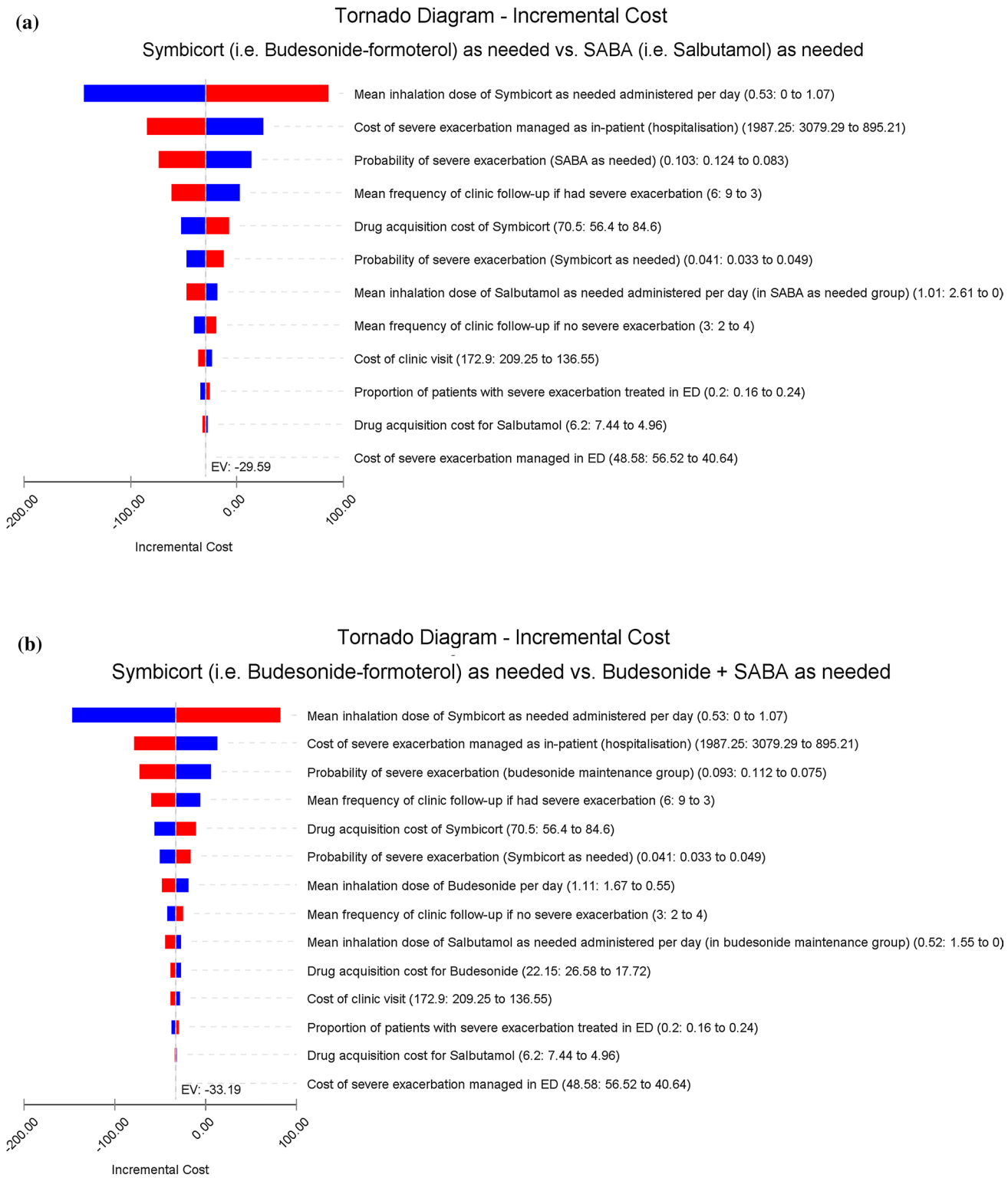

Fig. 4 Tornado diagram for Symbicort® PRN versus **a** SABA PRN and **b** budesonide BID + SABA PRN (real-world setting). *BID* twice daily, *ED* emergency department, *PRN* as needed, *SABA* short-acting β_2-agonist

medicine, and its low acquisition cost have also led to over-reliance on these relievers. However, overuse of these relievers has been associated with more AEs, poor asthma control, and adverse clinical outcomes, including severe exacerbations and deaths [25–29].

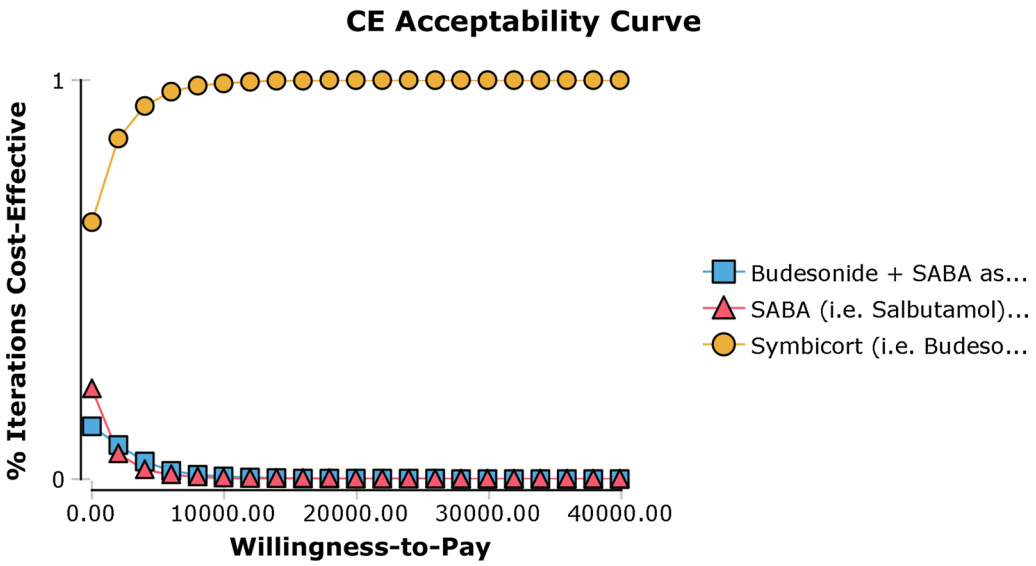

Fig. 5 Cost-effectiveness acceptability curve (real-world setting). *CE* cost effectiveness, *SABA* short-acting β_2-agonist

The 2019 GINA guidelines saw remarkable shifts in the management of patients with mild asthma, with the emerging body of evidence suggesting the unsafe overuse of SABA alone in the absence of concomitant controllers [1]. In the current model, three asthma treatment strategies of clinical relevance for patients with mild asthma in the Malaysian setting were compared. Although the GINA 2019 guidelines do not recommend using SABA alone for treatment, this comparator was included as one of the alternatives in the current model to better reflect local clinical practice in the Malaysian setting. Therefore, the model applied in the current study is in accordance with local clinical practice, GINA 2019 guidelines, and the MOH *Clinical Practice Guidelines* [1, 6].

In the current model, the efficacy data (i.e. the annualised severe exacerbation rate) for all comparators were obtained from the published randomised controlled trial (RCT) SYGMA 1 [10]. Of note, the SYGMA 1 trial used terbutaline as a reliever, whereas in the Malaysian setting and thus the current model, salbutamol is the predominant choice of reliever therapy. It is important to note that the efficacy of terbutaline was found to be the same as that of salbutamol as a reliever therapy [18–20]. The indications for and administration of all comparators in these studies are similar to the current clinical practice in Malaysia, as agreed by the expert panel. Hence, the efficacy data and dosing regimen used in the SYGMA 1 trial were generalisable to the Malaysian setting.

Our results indicate that budesonide/formoterol PRN is a dominant treatment option for patients with mild asthma in the Malaysian setting when compared with SABA PRN despite the much higher drug acquisition cost of budesonide/formoterol. Compared with maintenance budesonide, treatment with budesonide/formoterol PRN was associated with an ICER of RM696.11 per severe exacerbation avoided. Two large RCTs (i.e. SYGMA 1 and 2) involving more than 8000 patients demonstrated that budesonide/formoterol PRN was non-inferior to daily low-dose maintenance ICS (budesonide) in combination with SABA PRN in preventing severe exacerbations [10, 11]. In addition, it is important to note that the observed positive effects with budesonide/formoterol PRN in both SYGMA trials were achieved at a much lower median daily dose of inhaled glucocorticoid (i.e. only 17–25% of that in the maintenance budesonide group) [10, 11, 30]. One asthma management goal is to prevent exacerbations with the minimal use of medications, particularly the lowest ICS load [1]. Hence, the much lower glucocorticoid dose associated with a budesonide/formoterol PRN regimen would reduce the risk of developing glucocorticoid side effects and improve treatment acceptability among glucocorticoid-averse patients. Of note, although the use of ICS may increase the risk of systemic corticosteroid AEs, such as hypothalamic-pituitary-adrenal axis suppression, growth suppression in children, osteoporosis, infection/pneumonia, cataract/glaucoma, and skin thinning/bruising, AE management costs were not included in the current model as these AEs are generally associated with long-term ICS use (usually more than 1 year) [31], which is beyond the current model's time horizon. Furthermore, inclusion of these cost consequences would further strengthen the economic advantage of budesonide/formoterol PRN and would not change the model's outcomes.

To date, only one CEA of budesonide/formoterol PRN has been published, and this was conducted from the

perspective of the UK payer [32]. That study reported budesonide/formoterol PRN to be a dominant intervention, with a cost saving of £292.99 and a quality-adjusted life-year (QALY) gained of 0.001 when compared with maintenance budesonide. Although that CEA modelled for a 70-year time horizon, it was limited by extrapolation of the efficacy data beyond 1-year follow-up, which poses great uncertainty, particularly with the relatively new strategy in employing budesonide/formoterol PRN in mild asthma. It also did not explore whether the demonstrated efficacy of budesonide/formoterol could translate to effectiveness, given that patient adherence to maintenance ICS therapy in the pragmatic setting is usually much lower than in controlled trials. For instance, in the Novel START trial, the mean rate of adherence to twice-daily maintenance budesonide therapy was merely 56%, a possible attributing factor to the higher number of severe exacerbations being reported in the maintenance budesonide group. This issue was addressed in the current CEA by using data from the Novel START trial. We showed that budesonide/formoterol PRN was a dominant intervention compared with maintenance budesonide. Other than the aforementioned CEA, only one budget impact analysis (BIA) of budesonide/formoterol PRN has been conducted [33]. In that BIA, the introduction of budesonide/formoterol PRN as one of the treatment options for patients with mild asthma in Egypt was associated with a total budget saving of 3.038 billion Egyptian pounds over 3 years. Although there would be an increase in the drug cost upon the introduction of budesonide/formoterol PRN, this would be offset by reducing the total costs of healthcare resource utilisation.

Taken together, the currently available CEAs and BIAs conducted in different regions of the world demonstrated that budesonide/formoterol PRN was a cost-saving or dominant strategy in treating patients with mild asthma. In the PRACTICAL trial, ethnicity played no part in the finding that budesonide/formoterol PRN was more effective than maintenance budesonide in preventing severe exacerbations, at least between Māori and Pasifika adults and New Zealand European/other [34]. Although drug acquisition costs and the costs of asthma management may vary between countries, sensitivity analysis demonstrated that the model outcome was insensitive in the Malaysian setting when these parameters were varied. This suggests that the current findings could be extended, providing the healthcare system resources/utilisation costs/structures are similar to the setting depicted in the current study.

Nevertheless, it is important to highlight that the SYGMA and Novel START trials had some differences. The Novel START trial recruited patients with milder symptoms (mild intermittent asthma) than the SYGMA trials. A withdrawal of low-dose inhaled glucocorticoid therapy or leukotriene-receptor antagonist therapy involving the majority of the participants during the run-in phase in the SYGMA trials could potentially lead to poorer asthma control in participants, even before the start of the trial. It is currently unclear how this difference in the asthma control status of these trials could affect the probability of severe exacerbations, the most influential factor for the ICER between budesonide/formoterol PRN and maintenance budesonide treatments. However, it has been shown that budesonide/formoterol PRN was less effective than maintenance budesonide/formoterol plus SABA PRN in the management of moderate stable asthma [35].

As illustrated in Fig. 2a, b, one-way sensitivity analyses revealed that the model's outcomes were most sensitive to the changes in the mean inhalation of budesonide/formoterol PRN administered per day (Fig. 2a) and the probability of a severe exacerbation in the maintenance budesonide group (Fig. 2b). When the model was populated with data from the Novel START trial (Fig. 4a, b), the mean inhalation of budesonide/formoterol PRN administered per day remained the factor that most affected the model's outcomes, followed by the cost of managing severe exacerbations in a hospital setting. This result could be due to the wide plausible range of mean inhalation of budesonide/formoterol PRN administered daily and the cost of managing severe exacerbations in hospital. The lower range value of the probability of severe exacerbations in the maintenance budesonide group had substantial influence on the model's outcomes (Fig. 2b) because of the very small incremental effectiveness between the comparators. The cost of managing severe exacerbations in the emergency department had the least impact on both model outcomes. This is not surprising given the reported low cost of managing severe exacerbations in the emergency department (i.e. RM48.58 per exacerbation) and the smaller proportion of patients with severe exacerbations treated in the emergency department (i.e. 20%) in the Malaysian setting.

There are several limitations to the present model. The use of expert opinions may be subject to unintentional bias. However, this approach is commonly used when no other data are available [21]. Furthermore, the one-way sensitivity analysis performed in the current study showed that the model's outcomes were generally robust to the expert panel's estimates. Furthermore, intermediate rather than final health outcomes (i.e. patient quality of life) were presented in the current model. This is because most RCTs, including those used in the current model (i.e. SYGMA 1 and 2), did not define the final health outcome as the primary efficacy outcome measure. Lastly, the time horizon used in the present study was limited to 1 year because the clinical trials investigating the efficacy of budesonide/formoterol PRN followed-up patients for only 52 weeks. A future study evaluating the cost effectiveness of budesonide/formoterol PRN for a longer time horizon is anticipated.

Conclusions

From the Malaysian healthcare payer perspective, budesonide/formoterol PRN is either a dominant or likely to be a cost-effective treatment option for patients with mild asthma when compared with SABA PRN or maintenance budesonide treatments.

Declarations

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Conflict of interest V. Raja Gopal, N. S. I. Abdullah Thani, and W. Tan are employees of AstraZeneca (Malaysia) Sdn. Bhd., Selangor, Malaysia.

Ethics approval Not applicable.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to participate/Consent for publication Not applicable.

Author contributions CF Neoh constructed the economic model, was involved in data analysis and validation, and drafted the manuscript. VRG, NSIAT, and WT reviewed the content of the manuscript. All authors read and approved the final manuscript.

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