

Cost-effectiveness of indacaterol/glycopyrronium in comparison with salmeterol/fluticasone combination for patients with moderate-to-severe chronic obstructive pulmonary disease: a LANTERN population analysis from Singapore

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INTRODUCTION In light of the growing evidence base for better clinical results with the use of the dual bronchodilator indacaterol/glycopyrronium (IND/GLY) over inhaled corticosteroid-containing salmeterol/fluticasone combination (SFC), this study aimed to evaluate the cost-effectiveness of IND/GLY over SFC in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) who are at low risk of exacerbations, in the Singapore healthcare setting.

METHODS A previously published patient-level simulation model was adapted for use in Singapore by applying local unit costs. The model was populated with clinical data from the LANTERN and ECLIPSE studies. Both costs and health outcomes were predicted for the lifetime horizon from a payer's perspective and were discounted at 3% per annum. Costs were expressed in 2015 USD exchange rates. Uncertainty was assessed through probabilistic sensitivity analysis.

RESULTS Compared to SFC, use of IND/GLY increased mean life expectancy by 0.316 years and mean quality-adjusted life years (QALYs) by 0.246 years, and decreased mean total treatment costs (drug costs and management of associated events) by USD 1,474 over the entire lifetime horizon. IND/GLY was considered to be 100% cost-effective at a threshold of 1 × gross domestic product per capita. The cost-effectiveness acceptability curve showed that IND/GLY was 100% cost-effective at a willingness-to-pay threshold of USD 0 (additional cost) when compared to SFC.

CONCLUSION IND/GLY was estimated to be highly cost-effective compared to SFC in patients with moderate-to-severe COPD who are not at high risk of exacerbations in the Singapore healthcare setting.

Keywords: COPD, cost-effective, indacaterol/glycopyrronium, salmeterol/fluticasone, Singapore

INTRODUCTION

Morbidity and mortality associated with chronic obstructive pulmonary disease (COPD) are considerably high. According to the Global Burden of Disease Study, COPD was the fifth leading cause of years lived with disability and the third leading cause of death in 2010.^(1,2) Currently, COPD is the tenth leading cause of death in Singapore.⁽³⁾ Across the Asia-Pacific region, the overall prevalence of COPD was estimated to be 6.2% in 2012, and in Singapore alone, this rate was 5.9%.⁽⁴⁾

The economic burden of COPD in Singapore is considerably high. During 2005–2009, the total direct medical costs associated with COPD were estimated to be USD 9.9 million per year, with hospitalisations accounting for over 70% of the amount,⁽⁵⁾ implying that reducing hospitalisations or, specifically, reducing the frequency of exacerbations and pneumonia can significantly decrease the associated financial burden.

It has been observed that approximately 70% of patients have COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage I or II (largely falling into the GOLD Group B category) at the time of diagnosis.⁽⁶⁾ The GOLD guidelines recommend the use of inhaled corticosteroids (ICSs) in

combination with a long-acting β_2 -adrenergic agonist (LABA) and/or a long-acting muscarinic antagonist (LAMA) for patients with severe or very severe airflow limitation and/or ≥ 2 exacerbations per year or ≥ 1 exacerbation per year leading to hospital admission (Groups C and D).⁽⁷⁾ Despite these recommendations, ICSs are widely used for as many as one-third of GOLD Groups A and B patients with mild or moderate airflow limitation and/or 0–1 exacerbation per year with no hospitalisation for exacerbation.^(8–13) The overuse of ICSs increases the risk of side effects in these patients,^(7,14–18) thereby increasing the healthcare costs of COPD management.^(7,8,13,14)

The dual bronchodilator indacaterol/glycopyrronium (IND/GLY), a combination of LABA (indacaterol) and LAMA (glycopyrronium), is approved for maintenance treatment of COPD in Singapore. The use of IND/GLY is indicated for patients who remain symptomatic despite being on long-acting monotherapy and have a history of infrequent exacerbations.⁽⁷⁾ Randomised controlled trials, such as ILLUMINATE⁽¹⁹⁾ and LANTERN,⁽²⁰⁾ have compared IND/GLY to the LABA/ICS-containing combination of salmeterol/fluticasone (SFC), considering them as appropriate comparators, in largely low-risk but symptomatic patient

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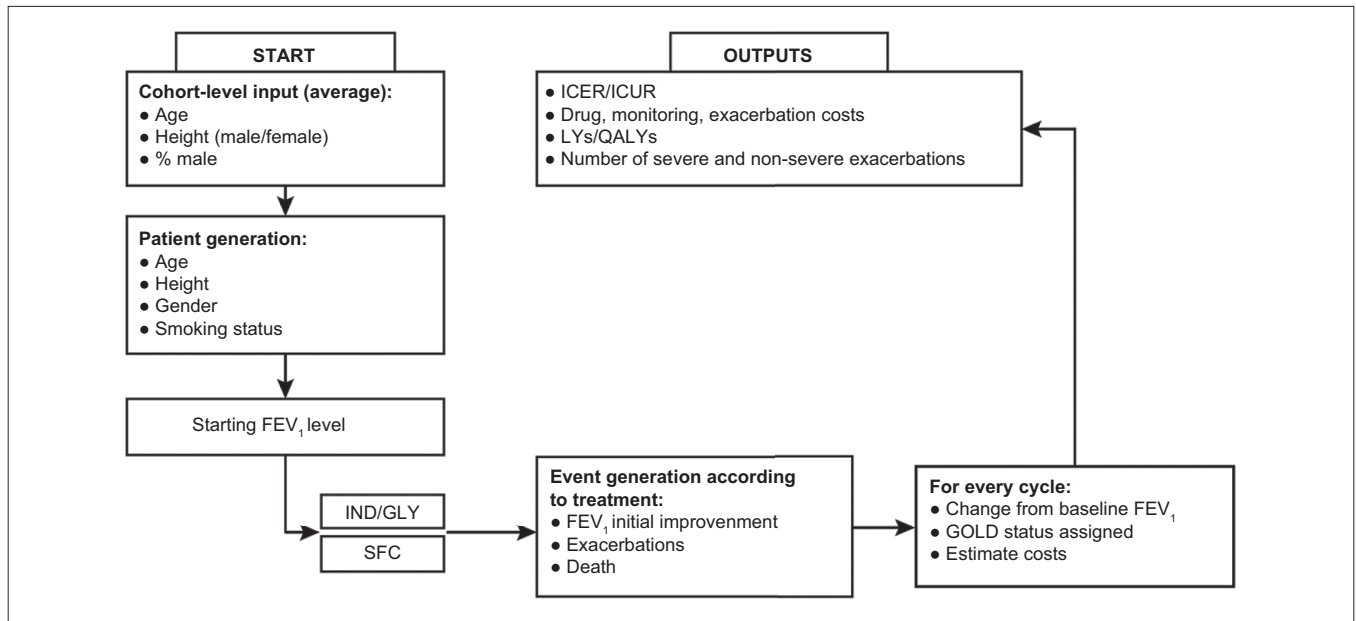


Fig. 1 Flowchart shows the schematic model used for the comparison of costs and outcomes of COPD patients managed with IND/GLY versus SFC. COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; IND/GLY: indacaterol/glycopyrronium; LY: life year; QALY: quality-adjusted life year; SFC: salmeterol/fluticasone

populations with moderate-to-severe COPD.^(19,20) Although the guideline recommends the use of SFC for severe or very severe COPD (GOLD Groups C and/or D) with a history of repeated or severe exacerbations,⁽⁷⁾ it is commonly used in low-risk patients in real-life practice.⁽⁸⁻¹³⁾ Evidence from the recently concluded LANTERN trial suggests that when compared to SFC, IND/GLY significantly reduced the rate of moderate or severe exacerbations by 31% in symptomatic GOLD Group B and D (53% and 47% of the total population, respectively) patients with a history of ≤ 1 exacerbation in the previous year (based on modified medical research council scores and lung function criteria).⁽²⁰⁾ In addition, the incidence of pneumonia was observed to be lower with IND/GLY than with SFC. Based on these new clinical findings from the LANTERN trial, the current study aimed to evaluate the pharmacoconomics of IND/GLY and SFC among patients with moderate-to-severe COPD and a history of ≤ 1 exacerbation in the previous year in a Singapore healthcare setting.

METHODS

Changi General Hospital (CGH) is a public, tertiary acute hospital located in the eastern region of the island state of Singapore.⁽²¹⁾ It is a 1,000-bedded hospital that serves a population of about one million people. Singapore healthcare has a mixed financing model, comprising a combination of out-of-pocket payments by the individual, individual insurance, mandatory personal medical savings accounts (Medisave), mandatory health insurance that covers catastrophic inpatient admission episodes (MediShield Life) and government subsidies for healthcare services through public healthcare institutions.⁽²²⁾

A previously published patient-level simulation model^(23,24) was used to compare the costs and outcomes of patients with COPD managed with IND/GLY and SFC from the public healthcare perspective in Singapore (Fig. 1). Data from published trials was

used for validating the model, as described in the previously published paper.⁽²³⁾ A cohort of patients ($n = 100,000$) was generated, where each patient was assigned a unique set of baseline characteristics using mean values and variance-covariance matrices derived from patient-level trial data. Using Monte Carlo simulation methods, a simulated patient moved through the model. The patient experienced clinical events, complications and progression at probabilities based on their simulated baseline characteristics and treatment-specific risk modifiers. The model incorporated the effects of forced expiratory volume in one second (FEV₁) decline, exacerbation and pneumonia event rates. For each patient, the initial FEV₁ score was based on their simulated characteristics and the treatment they were distributed to. The decline in FEV₁ was calculated as described by Falaschetti et al⁽²⁵⁾ and the European Community for Steel and Coal.⁽²⁶⁾ As FEV₁ declined, patients moved into GOLD states of increasing severity. Thus, disease severity was determined at each cycle of six months based on GOLD states. A simulated patient could die according to life table mortality probabilities if their simulated FEV₁ fell to less than 0 or if a patient survived to 100 years of age.

Detailed descriptions of the parameters used in the model have been provided in the previously published paper.⁽²³⁾ However, two parameters, the Transition Dyspnea Index and St George's Respiratory Questionnaire, were not considered for the present cost-effectiveness analysis, as these were more related to treatment switching. Since the comparator was an ICS combination, pneumonia rates and costs were later added to the model due to the established evidence of risk of pneumonia with ICS use.⁽¹⁷⁾

The cycle lengths were set to six months to match the study duration of the LANTERN trial and the time horizon was a lifetime. Results were also presented for one year, three years, five years and ten years to better inform healthcare policies on

the short-, medium- and long-term benefits of the use of IND/GLY over SFC in Singapore. Health outcomes were expressed in terms of life-years (LYs) and quality-adjusted LYs (QALYs), and were used to calculate the incremental cost-effectiveness ratios and the incremental cost-utility ratios.

The model was updated with the population and clinical data from the LANTERN study⁽²⁰⁾ and adapted for use in the Singapore healthcare setting. The LANTERN study was a 26-week, multicentre, randomised, double-blind, double-dummy, parallel-group study, which aimed to assess the efficacy, safety and tolerability of IND/GLY when compared to SFC in patients with moderate-to-severe COPD with a history of ≤ 1 exacerbation in the previous year. The population and efficacy inputs used for comparison are summarised in Tables I and II.

Since the analysis took on the healthcare provider's perspective, only direct costs were included, which comprised COPD drugs, maintenance costs, and costs related to exacerbations and pneumonia events. Maintenance costs were defined as non-exacerbation-related costs after deducting the costs of COPD drugs. Inpatient costs were based on actual admission gross bills incurred at CGH for the respective disease-related groups. Outpatient costs were based on specialist treatment costs at CGH.

Table I. Population inputs from the LANTERN trial.⁽²⁰⁾

Baseline characteristic	Mean \pm SD/%
Age at baseline (yr)	65.1 \pm 7.93
Height (cm)	165.7 \pm 7.16
Male gender	90.7
Body mass index (kg/m ²)	23.80 \pm 3.77
Patients according to disease severity	
GOLD I (80%–100%)	0.1
GOLD II (50%–80%)	52.2
GOLD III (30%–50%)	46.4
GOLD IV (0%–30%)	1.3

GOLD: Global Initiative for Chronic Obstructive Lung Disease; SD: standard deviation

Table II. Efficacy inputs derived from the LANTERN trial.⁽²⁰⁾

Parameter	Least square means (95% CI)	
	IND/GLY	SFC
FEV ₁ improvement after 6 mth* (L)	0.162 (0.129–0.195)	0.055 (0.022–0.088)
Pneumonia rate [†]	0.017 (0.003–0.040)	0.057 (0.028–0.096)
Exacerbation rate[‡]		
No history of exacerbations	0.230 (0.164–0.332)	0.334 (0.262–0.409)
1 exacerbation in past year	0.515 (0.358–0.739)	0.747 (0.587–0.916)
≥ 2 exacerbations in past year	1.316 (0.915–1.888)	1.908 (1.499–2.340)
Probability of severe/non-severe exacerbation (%)		
	Non-severe	Severe
GOLD I	100.0	0.0
GOLD II	94.5	5.5
GOLD III	92.4	7.6
GOLD IV	87.5	12.5

*Improvement in trough FEV₁ from baseline. [†]Annualised rate of pneumonia-related hospitalisation. [‡]Annualised rate of moderate-to-severe exacerbation. CI: confidence interval; FEV₁: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IND/GLY: indacaterol/glycopyrronium; SFC: salmeterol/fluticasone

In addition, costs of primary care follow-up were estimated from the Primary Care Survey 2010.⁽²⁷⁾

Resource use estimates were obtained from a German study⁽²⁸⁾ and, where appropriate, provided by local experts. All resource use estimates were validated by local experts for use in the Singapore healthcare setting (Table III). Singapore-specific unit costs were applied to the resource use data to calculate the costs in USD. The cost base year was 2015. The exchange rate used was 1 USD = 1.4 SGD.⁽²⁹⁾ Aggregated maintenance costs for different severity stages were estimated as follows (in USD): mild (USD 82.2); moderate (USD 83.4); severe (USD 145.6); and very severe (USD 229.5). The total costs were assessed to be USD 57.1 for non-severe exacerbations and USD 1,661.0 for severe exacerbations. Both costs and health outcomes were annually discounted at a rate of 3%.

The rates of mild, moderate and severe COPD exacerbations were obtained from the LANTERN study. The baseline exacerbation rate for patients treated with IND/GLY with no previous history of exacerbations was estimated to be 0.23 (95% confidence interval [CI] 0.16–0.33). However, increase in the future risk of exacerbations, associated with a history of previous exacerbations,^(30–34) was estimated using data from the ECLIPSE study (which included both exacerbators and non-exacerbators): 2.24 (95% CI 1.17–4.47) for patients with a history of one exacerbation; and 5.72 (95% CI 2.84–7.31) for patients with a history of ≥ 2 exacerbations in the past year.⁽³⁰⁾ Data from the LANTERN study could not be used, as it excluded patients who were frequent exacerbators (≥ 2 exacerbations in the past year). The exacerbation rate ratio for SFC versus IND/GLY was estimated to be 1.45 (95% CI 1.10–1.97), which was based on data from the LANTERN trial (pertaining to both patients with and without exacerbation history). This rate ratio was applied over the lifetime horizon of the model and to all severity stages. As also mentioned in Asukai et al,⁽²³⁾ it was assumed that continued treatment returned a continued treatment effect based on the results of the one-year SPARK trial⁽³⁵⁾ and FLAME trial.⁽³⁶⁾ It was also

Table III. Resource inputs and costs used in the analysis.

Variable	Annual resource rates for maintenance				Per episode for exacerbations		Unit cost* (USD)
	Mild	Moderate	Severe	Very severe	Non-severe	Severe	
Influenza vaccination (no. of injections)	1.0	1.0	1.0	1.0	–	–	11.40
Theophylline (days/patient)	0.0	122.10	161.80	159.10	–	–	0.10
Mucolytics (days/patient)	0.0	39.70	48.30	80.60	–	–	0.50
Oral corticosteroids (days/patient)	0.0	21.50	23.70	78.50	5.0	5.0	0.40
Oxygen (% patients)	0.0	0.0	0.0	0.20	–	–	454.20
GP visit*	2.0	–	–	–	–	–	45.10
Specialist outpatient visit	–	1.0	3.0	4.0	1.0	–	50.70
Spirometry (no. of tests)	1.0	1.0	1.0	1.0	–	–	62.90
Antibiotics (days/patient)	–	–	–	–	5.0	5.0	0.90
ER visit with admission	–	–	–	–	–	1.0	82.10
Non-ICU hospital stay	–	–	–	–	–	1.0	1,572.40
Pneumonia cost†	–	–	–	–	–	–	3,137.90
Drug cost (daily)							
IND/GLY	–	–	–	–	–	–	1.38
SFC	–	–	–	–	–	–	1.44

*Cost base year was calculated based on details available as of 27 August 2015. †GP visit included treatment/investigations and consultation. ‡Refers to the occurrence of a pneumonia event. ER: emergency room; ICU: intensive care unit; IND/GLY: indacaterol/glycopyrronium; GP: general practitioner; SFC: salmeterol/fluticasone

Table IV. Incremental results for the base case cost-effectiveness analysis for IND/GLY versus SFC.

Variable	Time horizon				
	1 yr	3 yr	5 yr	10 yr	Lifetime
Total incremental cost (USD)	–104	–360	–606	–1,084	–1,474
Drug	–22	–56	–81	–110	–69
Maintenance	–7	–21	–31	–53	–39
Non-severe exacerbation	–4	–25	–53	–115	–179
Severe exacerbation	–9	–52	–114	–255	–412
Pneumonia	–62	–206	–326	–551	–776
Incremental LY	0.000	0.008	0.025	0.091	0.316
Incremental QALY	0.001	0.012	0.030	0.089	0.246
ICER	Dominant	Dominant	Dominant	Dominant	Dominant
ICUR	Dominant	Dominant	Dominant	Dominant	Dominant

ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; IND/GLY: indacaterol/glycopyrronium; LY: life year; QALY: quality-adjusted life year; SFC: salmeterol/fluticasone

assumed that the treatment effect observed in the LANTERN trial was applicable to patients who later experienced more frequent exacerbations. Pooled data of indacaterol trials was used to derive the probabilities of severe or non-severe exacerbations based on disease severity in terms of the patient's GOLD stage.⁽³⁷⁻³⁹⁾

The regression method reported by Rutten-van Mólken et al⁽⁴⁰⁾ and Price et al⁽²⁴⁾ was used to derive the utility values. Inputs for the regression model were taken from within the model or assumed from the ECLIPSE study where not available.⁽³⁰⁾ The following regression equation was used to calculate the utility value at each cycle, where the number of concomitant diseases was assumed to be four per person: Utility value = 0.688 + (gender × 0.057) + (FEV₁% predicted × 0.003) + (emergency visits in the last year × –0.029) + (hospital admission in the last year × –0.02) + (number of concomitant diseases × –0.01) + (body mass index × –0.003).

To accurately reflect the characteristics of patients with COPD in Singapore, age-related mortality rates were calculated using the general population mortality rates in Singapore,⁽⁴¹⁾ though these were based on population characteristics from the LANTERN study. COPD-related mortality rates were calculated by applying a hazard ratio of 1.02 (deduced from the OLIN COPD study),⁽⁴²⁾ which described the increased risk of death associated with a decline in FEV₁.⁽⁴²⁾ This hazard ratio was adjusted based on the predicted decline in FEV₁ for an individual patient⁽²⁵⁾ using the following equation, where the mortality rate was based on FEV₁ status and not the exacerbation rate: Probability of death = (general population risk for the appropriate age and gender) × 1.02 (the decline in FEV₁% predicted).

Probabilistic sensitivity analysis was conducted to assess the uncertainty with regard to the estimated values. The analysis was performed using 10,000 patients and 1,000 cohorts.

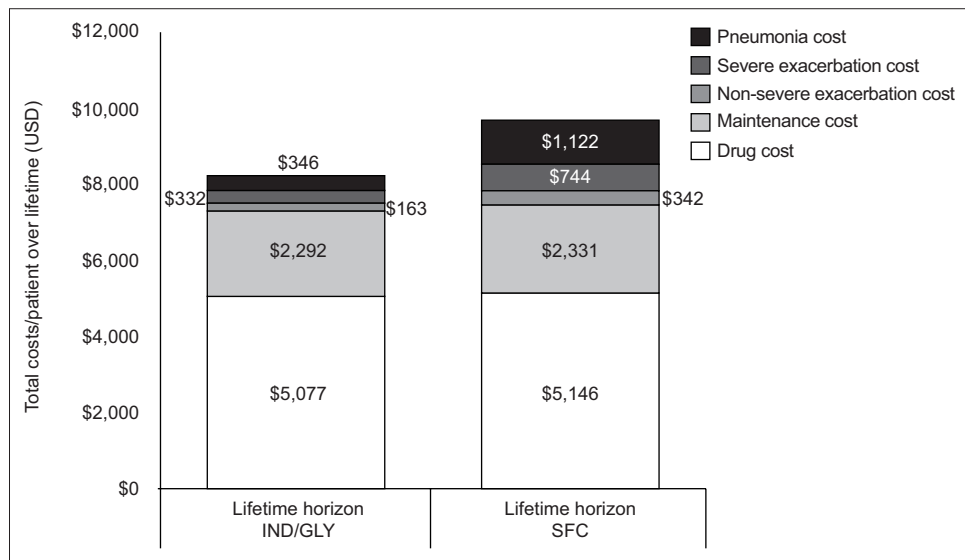


Fig. 2 Bar chart shows costs per patient (in USD) over the lifetime horizon for IND/GLY and SFC. IND/GLY: indacaterol/glycopyrronium; SFC: salmeterol/fluticasone

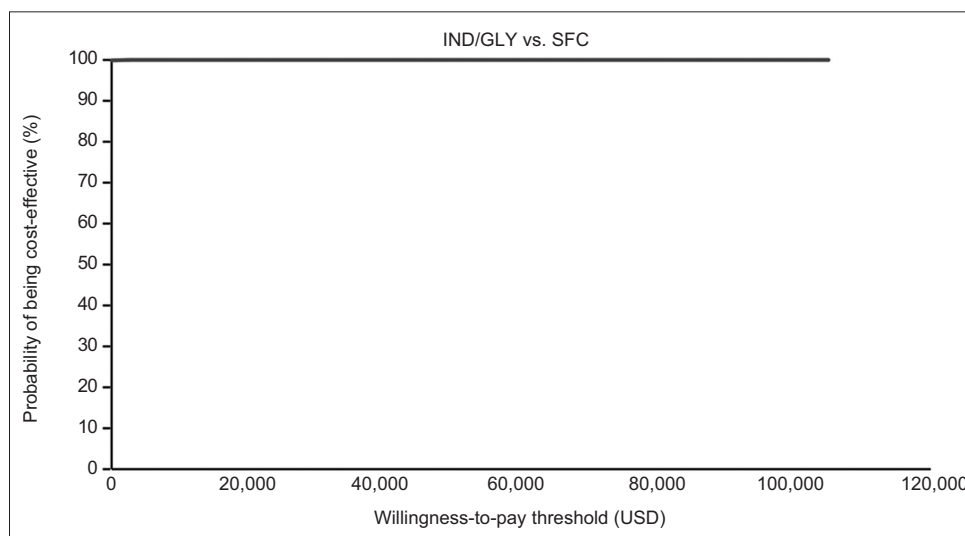


Fig. 3 Chart shows the cost-effectiveness acceptability curve of IND/GLY and SFC. IND/GLY: indacaterol/glycopyrronium; SFC: salmeterol/fluticasone

RESULTS

Results of the base case cost-effectiveness analysis of all time horizons are presented in Table IV. Our analysis indicated that patients on IND/GLY had better health-related quality of life (incremental QALYs 0.246) and experienced gain in LYs (incremental LYs 0.316) when compared to those receiving SFC. This was accompanied by cost savings of USD 1,474 compared to SFC over the entire lifetime horizon. These results indicate that IND/GLY is a dominant treatment strategy over SFC, being more effective and less costly.

On comparing IND/GLY and SFC, the use of IND/GLY led to cost savings per patient over a lifetime for drug costs (USD 5,077 vs. USD 5,146), maintenance costs (USD 2,292 vs. USD 2,331), non-severe exacerbation costs (USD 163 vs. USD 342), severe exacerbation costs (USD 332 vs. USD 744) and pneumonia costs (USD 346 vs. USD 1,122) (Fig. 2). With these, total cost savings per patient over a lifetime was observed to be higher with the use of IND/GLY over SFC (USD 8,210 vs. USD 9,685).

Results of the probabilistic sensitivity analysis showed that at a threshold of zero, in 99.98% of simulations, the use of IND/GLY resulted in lower costs and more QALYs than SFC. The cost-effectiveness acceptability curve showed that IND/GLY was 100% cost-effective at a willingness-to-pay threshold of USD 0 (additional cost) when compared to SFC (Fig. 3).

DISCUSSION

This analysis demonstrated the economic value of IND/GLY in the Singapore healthcare setting at CGH based on data from the LANTERN and ECLIPSE studies. The base case analysis results indicated that IND/GLY was a dominant (more effective and less costly) treatment strategy over SFC in a Singapore patient population that was not at high risk for exacerbation, similar to that of the LANTERN study. This conclusion was based on the WHO-CHOICE (World Health Organization-Choosing Interventions that are Cost-Effective) method developed using gross domestic product (GDP) per capita (< 1 GDP per capita:

very cost effective; 1–3 × GDP per capita: cost effective; > 3 × GDP per capita: not cost effective; Singapore's GDP per capita in 2015 was USD 56,285).^(43,44) IND/GLY was observed to be 100% cost-effective at a threshold of 1 × GDP per capita.

IND/GLY was associated with lower drug costs, maintenance costs, non-severe exacerbation costs, severe exacerbation costs and much lower pneumonia costs when compared to SFC for the treatment of patients with COPD in Singapore over a lifetime horizon. The results were consistent across the various time horizons analysed – one, three, five and ten years – with greater cost savings and more benefits, in terms of QALYs and LYs, observed at the extended time horizons.

To the best of our information, this is the first study to assess the cost-effectiveness of IND/GLY versus SFC in a broad patient population with COPD (patients with moderate-to-severe COPD with a history of ≤ 1 exacerbation in the previous year) in the Singapore healthcare setting. However, this analysis has several limitations. First, the LANTERN trial had a short study duration of 26 weeks, which was not adequate to measure exacerbations as a primary endpoint. Second, although the LANTERN trial included a broad patient population, patients who had frequent exacerbations (> 1 exacerbation in the prior year) were not included. Third, this analysis was based on a single randomised controlled clinical trial. A comprehensive assessment to extrapolate our findings to the entire patient population with COPD would require inclusion of data points of IND/GLY versus SFC from other sources (e.g. multiple trials or data from real-world studies that are specific to the Singapore COPD population). Fourth, data from the ECLIPSE study was used to link exacerbation history and the likelihood of future exacerbations, instead of data from the LANTERN trial, which provided all the other population and clinical data for populating the model.

Due consideration was given to the fact that the population inputs of the LANTERN trial should be used, as this would best reflect and model the observed outcomes of the LANTERN trial. The LANTERN trial population comprised GOLD Group B patients (53% of the total population). As discussed earlier, approximately 70% of patients were classified as GOLD Stage I or II (largely GOLD Group B) at the time of diagnosis.⁽⁶⁾ However, in the real world, a high proportion (approximately 50%) of these GOLD Group B patients are managed with ICS-inclusive options,⁽⁹⁾ even though the use of ICS-containing combinations such as SFC are deemed inappropriate according to the GOLD guidelines of 2015 and 2017.^(7,45) Hence, although these results cannot be applied to the overall COPD population, it is quite relevant to a significant proportion of COPD patients in the real world. Furthermore, these populations and clinical inputs were validated by local experts for use in the Singapore patient population. Lastly, with regard to limitations, although resource utilisation rates, particularly for drug use, were estimated from a German study,⁽²⁸⁾ local experts adapted these to local clinical management practices.

The findings of our study are similar to those reported in other healthcare settings. The earlier cost-effectiveness analyses conducted in Swedish⁽²⁴⁾ and Greek⁽⁴⁶⁾ healthcare settings (both

based on clinical results from the ILLUMINATE trial)⁽¹⁹⁾ also demonstrated that IND/GLY was a dominant treatment over SFC in patients with COPD with and without a history of exacerbations. Further, a recently published cost-effectiveness analysis based on the LANTERN data reported that IND/GLY was more effective and less costly than SFC for patients with a history of ≤ 1 exacerbation in the previous year in four healthcare settings, namely Canada, France, Italy and Portugal.⁽⁴⁷⁾

In conclusion, this study suggests that IND/GLY is cost-effective when compared to SFC for patients with no exacerbation or those at low risk of exacerbation, similar to the patient population assessed in the LANTERN study, over the lifetime horizon in the Singapore healthcare setting. With the use of IND/GLY over SFC, health benefits were observed in terms of QALYs and LYs and there were cost savings in terms of drug, maintenance, exacerbation and pneumonia costs. This indicates that the use of IND/GLY, as opposed to SFC, offers the potential to reduce the economic burden of COPD in Singapore.

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