

Cost-effectiveness of tiotropium versus glycopyrronium in moderate to very severe chronic obstructive pulmonary disease in Canada, Spain, Sweden, and the UK

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Objectives: Tiotropium (TIO), Spiriva® Handihaler®, is a well-established bronchodilator, LAMA (long acting muscarinic antagonist), for the treatment of moderate to very severe chronic obstructive pulmonary disease (COPD). Clinical evidence from the SPARK trial suggests that TIO is superior to glycopyrronium (GLY), Seebri® Breezhaler®, in terms of severe exacerbations. This modeling study assessed the cost-effectiveness of TIO versus GLY for Canada (CAN), Spain (ESP), Sweden (SWE), and the UK, making use of this new clinical evidence.

Methods: A Markov cohort model, with moderate to very severe (Global Initiative for Chronic Obstructive Lung Disease II–IV) COPD patients, was populated with efficacy data from the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) and SPARK trials as well as costs, utilities, and epidemiological data relevant for each country. Treatment efficacy was modeled as improvements in lung function, quality-adjusted life years (QALYs), and as a lowering of the risk of exacerbations (rate of exacerbations). Risks of exacerbations differed between cohorts based on data from SPARK. Health and cost outcomes were simulated over an approximate lifetime horizon, starting from the age of 65 years. Robustness of results was validated in deterministic sensitivity analyses.

Results: Over the lifetime horizon, patients treated with TIO accumulated –623 (CAN), 1,066 (ESP), 1,137 (SWE), and –169 (UK), respectively, in incremental costs (€2014). TIO generated better health outcomes compared to GLY in all countries, 0.21 (CAN), 0.25 (ESP), 0.23 (SWE), and 0.23 (UK) in incremental QALYs. The cost per QALY gained was found to be €4,281 and €1,137 for ESP and SWE, respectively, while TIO was found to be cost saving in CAN and the UK. The results were mainly driven by the relative risk of severe exacerbations found in SPARK (GLY/TIO relative risk: 1.43, 95% confidence interval: 1.05–1.97, $P=0.025$).

Conclusion: The results from this study show that TIO is a cost-effective treatment compared to GLY in moderate to very severe COPD. The cost per QALY is well below the existing implicit and explicit willingness-to-pay thresholds.

Keywords: COPD, exacerbations, tiotropium, glycopyrronium, cost-effectiveness, Markov cohort model

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease affecting ~5%–10% of the adult population.^{1–4} In the European Union, COPD stands

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for 56% of the direct costs associated with respiratory diseases.⁵ Respiratory diseases, in turn, represent 6% of the total health care budget.⁵ This means that the estimated total cost of COPD in the European Union is €38.6 billion.⁵ In the US, the calculated annual direct cost burden of COPD amounts to \$30 billion.⁶ In addition to the high direct cost burden, indirect costs are large and amount to \$20 billion in lost production every year.⁶ Exacerbations, that is, “acute and sustained worsening of the patient’s respiratory symptoms beyond normal day-to-day variations that result in an increased need for medication [...]”, are important drivers of COPD-related costs.⁷ Exacerbations on the acute and severe end of the spectrum are the most common causes for COPD-related hospitalizations in the US and UK, and hospitalizations, in turn, represent 54% of direct COPD-related costs.^{8–10} Besides costs, exacerbations increase mortality^{11,12} and decrease health-related quality of life^{13,14} in COPD patients. Thus, COPD exacerbations represent a significant economic and clinical burden.

Pharmacologic therapy in moderate to severe COPD includes long-acting bronchodilators, long-acting β_2 agonists (LABAs), or LAMAs (long acting muscarinic antagonist). Inhaled corticosteroids (ICSs) and antibiotics can be used alone or in combination with bronchodilators to treat and mitigate the effects of exacerbations. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, the first choice of therapy for patients with moderate to severe COPD is LAMA or LABA therapy alone.⁵ In high-risk patients, that is, those at risk of exacerbations, ICS can be added to the LABA monotherapy. Short-acting bronchodilators, either in the form of an anticholinergic or a β_2 agonist, are typically administered as needed to relieve symptoms in the short term.

Several studies have shown that regular use of LAMAs, LABAs, and ICSs can lower the incidence and effect of exacerbations.¹⁵ In a 4-year, randomized, double-blind trial (Understanding Potential Long-term Impacts on Function with Tiotropium [UPLIFT]), tiotropium (TIO) significantly improved lung function (forced expiratory volume in 1 second [FEV₁]) and lowered the risk of exacerbations when added to usual non-LAMA care, compared to usual non-LAMA care alone.¹⁶ Evidence from recent studies also suggests that TIO is superior to both once-daily¹⁷ and twice-daily¹⁸ administered LABAs when it comes to preventing exacerbations. Furthermore, in a recent head-to-head trial (SPARK), patients treated with TIO had lower rates of severe exacerbations, that is, those leading to hospitalization, than patients treated with glycopyrronium (GLY).¹⁹

TIO has been shown to be a cost-effective treatment compared to usual care in the management of COPD in a number of countries.²⁰ However, evidence on the cost-effectiveness of TIO versus other LAMAs has been scarce. With the publication of SPARK results in addition to previous trials, it is now possible to compare TIO and GLY head-to-head.¹⁹ The primary objective of this study was to analyze the cost-effectiveness of TIO compared to GLY in Canada (CAN), Spain (ESP), Sweden (SWE), and the UK using data from the UPLIFT¹⁶ and SPARK¹⁹ trials.

UPLIFT and SPARK trials

UPLIFT¹⁶ was a randomized, double-blind, placebo-controlled study, investigating the efficacy of TIO when added to non-LAMA usual care (placebo) compared to placebo alone. A total of 5,993 patients (mean age, 65±8 years), with an FEV₁ of 70% or less, that is, moderate to very severe COPD (GOLD II–IV), after bronchodilation and a ratio of FEV₁ to forced vital capacity of 70% or less, were studied over a 4-year period. Co-primary end points were the rate of decline in mean FEV₁ before and after bronchodilation beginning on day 30. Secondary end points were, among other things, rates of exacerbations, measures of forced vital capacity, changes in St George’s Respiratory Questionnaire responses, and mortality. The main findings were that mean absolute improvements in FEV₁ in the TIO group were maintained throughout the trial as compared to placebo ($P<0.001$). In addition, the number of exacerbations per patient-year declined in favor of TIO.¹⁶

SPARK¹⁹ was a randomized parallel group study investigating the relative efficacy of QVA149 (GLY and indacaterol combination) versus GLY monotherapy and TIO monotherapy. A total of 2,224 patients were enrolled, aged 40 years or more, with severe or very severe COPD (GOLD III–IV) and one or more moderate COPD exacerbations in the last year. Results showed that there was no significant difference between GLY and TIO in preventing mild (GLY/TIO relative risk [RR]: 0.99, $P=0.90$) and moderate or severe (GLY/TIO RR: 1.03, $P=0.68$) exacerbations. However, in the case of severe exacerbations (SevEx) alone, TIO was superior to GLY (GLY/TIO RR SevEx: 1.43, $P=0.025$).

Methods COPD models

Chronic and slowly progressing diseases such as COPD are well characterized in a simple Markov cohort framework. Indeed, most cost-effectiveness models in the published COPD literature are Markov cohort models.^{7,21} In most cases,

model health states are constructed around the established GOLD classification of severity of airflow limitation.²² This classification is based on four groups: mild (GOLD I $FEV_1 \geq 80\%$), moderate (GOLD II $50\% \leq FEV_1 < 80\%$), severe (GOLD III $30\% \leq FEV_1 < 50\%$), and very severe (GOLD IV $FEV_1 < 30\%$) COPD, each representing an interval of post-bronchodilator FEV_1 , a measure of airflow.⁵ Some models^{23,24} also incorporate costs and effects of exacerbations, typically modeled as events occurring within the health (GOLD) states. This makes it possible to add baseline costs and outcomes associated with each health state as well as additional event-specific costs and outcomes associated with exacerbations. This study used data obtained from published sources of UPLIFT and SPARK trials. These trials had all the necessary regulatory and ethical approvals in place. As this is a modeling study without any primary data collected, we do not need regulatory/ethical approval.

Model description

The Markov cohort model, shown in Figure 1, was built in TreeAge Pro Suite 2014 and has been described before in an analysis for SWE.²⁵ The model was based on three health states (GOLD II, GOLD III, and GOLD IV), between which the cohort of patients could move with varying probabilities. Patients were modeled from the age of treatment initiation (65 years old) until they deceased or reached the end of the simulation (100 years). Two cohorts were analyzed, one receiving standard treatment with TIO 18 μ g (Spiriva® HandiHaler®) and one receiving standard treatment with GLY 44 μ g (Seebri® Breezhaler®). Upon entering the model, both

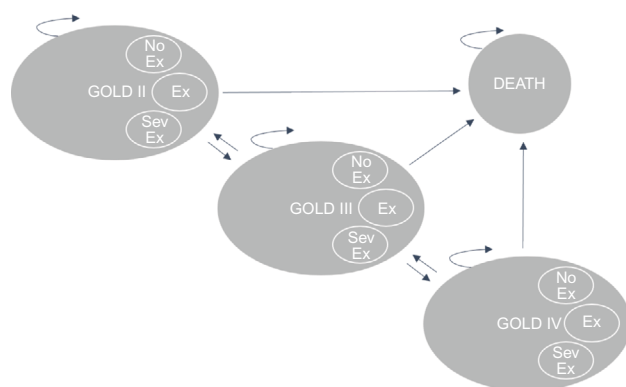


Figure 1 Markov model state transition diagram.

Note: The arrows reflect the fact that a patient can remain in the same state for several cycles.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOLD II, GOLD classification indicating moderate COPD; COPD, chronic obstructive pulmonary disease; GOLD III, GOLD classification indicating severe COPD; GOLD IV, GOLD classification indicating very severe COPD; No Ex, no exacerbation; Ex, exacerbation; SevEx, severe exacerbation.

cohorts of patients were distributed across the separate states according to the observed distributions found in UPLIFT (GII: 48%, GIII: 44%, GIV: 8%).¹⁶ Within each 3-month cycle, the patients could then experience any one of the following three events: 1) no exacerbation, 2) nonsevere exacerbation, or 3) severe exacerbation. Each event occurred with certain state-specific probabilities. Based on trial data from UPLIFT¹⁶ and SPARK,¹⁹ these probabilities were varied across the treatment alternatives in order to reflect relative efficacy of the treatment alternatives. Each state and event combination had different costs and effects associated with that particular combination. Subsequent to each event, the patients could either die or transition to one of the other two health states for a new 3-month cycle to begin. Within each state, a patient can experience any one of the following events: 1) no exacerbation (No), 2) nonsevere exacerbation (Ex), 3) severe exacerbation (Sev).

Target patient population

The base case model population was assumed to be similar to that of the UPLIFT¹⁶ trial in terms of age (65 years), disease state (GOLD II–IV), risks of exacerbations, and the usual (non-LAMA) care received besides the two treatment interventions modeled. In addition, to accurately reflect the real-world characteristics of COPD patients, the model was populated with mortality data representative for each country's patient population.

Clinical data

Transition probabilities and risks of exacerbations were mainly obtained from Hettle et al,²⁶ who in turn derived estimates from UPLIFT.¹⁶ GLY was assumed to be equivalent to TIO in terms of effects on overall lung function (FEV_1). The rationale for this assumption is well founded. Recent trials (GLOW1–2)²⁷ and indeed SPARK,¹⁹ as well as network meta-analyses,^{28,29} have shown comparability in terms of the effect on FEV_1 between TIO and GLY and other LAMAs. Thus, efficacy data (FEV_1) from the TIO arm of the UPLIFT trial was used to model disease progression in both the TIO and the GLY cohorts. However, data on RRs of exacerbations for TIO versus GLY were obtained from the SPARK¹⁹ trial. Table 1 provides an overview of the sources used to model treatment efficacy.

Hettle et al²⁶ derived sets of transition probabilities for TIO and usual care arms using data from UPLIFT. A separate set of transition probabilities was obtained for the first cycle on treatment in order to capture the initial 30-day effect of TIO on FEV_1 .²⁶ In the base case analysis, patients were assumed to be on treatment for 4 years from the start of simulation, based on the observed treatment duration in UPLIFT.¹⁶ The

assumption was made to ensure that results were not driven by unrealistic assumptions about treatment duration (some share of patients will in practice discontinue treatment). As there is little persistence in the effect of LAMAs after stopping treatment, transition probabilities were assumed to return to the placebo arm (usual care) probabilities from UPLIFT in the cycle after stopping treatment. The sets of transition probabilities used in the model are shown in Table 2.

Rates of exacerbations for usual care and TIO were obtained from Hettle et al²⁶ (derived from UPLIFT) and recalculated to reflect 3-month risks. RRs of exacerbations for TIO versus GLY were obtained from SPARK.¹⁹ Usual care probabilities were applied in cycles off treatment.

Table 3 shows the risks of different types of exacerbations by GOLD state for the two treatment alternatives as well as for cycles off treatment (usual care). The efficacy of

TIO versus GLY was modeled solely based on the risks of exacerbations observed in SPARK (GLY/TIO RR non-SevEx: 0.98 and GLY/TIO RR SevEx: 1.43).

Epidemiological data

Baseline age-differentiated mortality for the general population in each country was obtained from the national and World Health Organization databases on causes of deaths.³⁰⁻³³ From the databases, it was possible to discern the share of total deaths that were related to COPD and to factor these out of the baseline mortality rates for the general population. The corrected and age-differentiated mortality rates for the general population were then used as baseline rates, on top of which excess mortality related to COPD was added. Point estimates for excess mortality associated with each GOLD state were obtained from Garcia-Aymerich et al¹¹ and extrapolated over age intervals using the change in RR between age groups from Hoogendoorn et al.³⁴ Similarly, age-differentiated excess mortality rates for severe exacerbations were generated using point estimates and changes in RRs between age groups from Hoogendoorn et al.³⁴ Finally, it was assumed that “nonsevere

Table 1 Source overview of clinical inputs

Clinical input	TIO	GLY
Transition probabilities		
Cycles on treatment (year 0–4)	UPLIFT (TIO arm)	UPLIFT (TIO arm) ^a
Cycles off treatment (≥year 4)	UPLIFT (usual care arm) ^b	UPLIFT (usual care arm) ^b
Probabilities of exacerbations		
Baseline risks of exacerbations	UPLIFT (TIO arm)	UPLIFT (TIO arm)
RRs	(N/A baseline applied)	SPARK RR TIO/GLY ^c

Notes: ^aSeveral trials have shown comparable efficacy between tiotropium and glycopyrronium in terms of overall lung function (FEV₁). ^bAs there is little persistence in the effect of LAMAs after stopping treatment, transition probabilities were assumed to return to the placebo arm (usual care) probabilities in the cycle after stopping treatment. ^cApplied to baseline risks of exacerbations from UPLIFT (TIO arm). Adapted from Wedzicha et al¹⁹ and Hettle et al.²⁷

Abbreviations: TIO, Tiotropium; GLY, glycopyrronium; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium; N/A, not applicable; RR, relative risk; FEV₁, forced expiratory volume in 1 second.

Table 3 Model probabilities of exacerbations by GOLD states

Event/GOLD	Off treatment			Tiotropium			Glycopyrronium		
	II	III	IV	II	III	IV	II	III	IV
No exacerbation	0.84	0.78	0.73	0.87	0.81	0.77	0.86	0.79	0.74
Nonsevere exacerbation	0.14	0.17	0.18	0.11	0.14	0.15	0.11	0.14	0.14
Severe exacerbation	0.02	0.05	0.08	0.02	0.05	0.08	0.03	0.07	0.12

Notes: Usual care probabilities from UPLIFT were used in cycles off treatment. Probabilities reflect 3-month risks. Data from Hettle et al²⁷ (derived from UPLIFT), SPARK,¹⁹ and own calculations.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

Table 2 Model transition probabilities by GOLD states

		First cycle			Subsequent cycles		
		To			To		
		GOLD II	GOLD III	GOLD IV	GOLD II	GOLD III	GOLD IV
TIO/GLY							
From	GOLD II	0.92	0.08	0.00	0.92	0.08	0.00
	GOLD III	0.17	0.80	0.03	0.08	0.88	0.04
	GOLD IV	0.03	0.28	0.69	0.00	0.12	0.88
Off treatment							
From	GOLD II	0.86	0.13	0.01	0.91	0.09	0.00
	GOLD III	0.13	0.81	0.06	0.08	0.88	0.04
	GOLD IV	0.02	0.22	0.76	0.00	0.13	0.87

Notes: For TIO and GLY cohorts, usual care probabilities were assumed to hold when off treatment. Probabilities have been recalculated to reflect 3-month probabilities. Death has been excluded, as this model carries separate mortality rates derived for each country’s population. Based on own calculations using data from Hettle et al²⁷ (derived from UPLIFT¹⁶).

Abbreviations: GOLD II, GOLD classification indicating moderate COPD; COPD, chronic obstructive pulmonary disease; GOLD III, GOLD classification indicating severe COPD; GOLD IV, GOLD classification indicating very severe COPD; TIO, Tiotropium; GLY, glycopyrronium; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

exacerbations” did not additionally impact mortality, that is, the state-specific mortality rates were assumed to hold in cycles where these events occurred.

Health economic data

Drug costs for TIO and GLY were obtained from relevant sources in each country. The drug costs (€2014) per patient per day for each country are displayed in Table 4.

Direct costs, presented in Table 5, were assigned to the different state–event combinations. Each cycle that a patient spent in one of the GOLD states had an associated maintenance cost plus an extra cost for the particular event (no exacerbation, nonsevere exacerbation, or severe exacerbation) occurring during that cycle. The costs of exacerbations were obtained from relevant sources in each country.

The baseline utility weights for each GOLD state were obtained from relevant sources in each country. In the case of CAN, UK weights were used due to the lack of data on Canadian COPD patients. Decrements associated with nonsevere exacerbations (1.66%) and severe exacerbations (4.82%) were obtained from Hoogendorn et al.³⁴ The decrements refer to the annual utility loss of nonsevere and severe exacerbations, respectively. The utility weight associated with each state–event combination was recalculated to reflect the cycle length (3 months), and it was assumed that the decrements lasted for the entire duration of the model cycle. Table 6 shows the annual utility weights associated with each state–event combination.

Table 4 Drug costs (€2014) per patient per day for each country

Therapy/country	CAN	ESP	SWE	UK
Spiriva Handihaler (tiotropium 18 µg)	1.48	0.97	1.40	1.39
Seebri Breezhaler (glycopyrronium 44 µg)	1.21	0.94	1.15	1.14

Notes: Ex-rates 2014: CAN (C\$ to €: 0.68), Bank of Canada⁴⁰; SWE (SEK to €: 0.11), Sveriges Riksbank⁴¹; UK (£ to €: 1.24), Bank of England.⁴² Dosing: one capsule per day. Adapted from Ontario Drug Benefit Formulary³⁵ (CAN), botplus + deductions^{36,37} (ESP), the Dental and Pharmaceuticals Benefits Agency (TLV)³⁸ (SWE), and MIMS³⁹ (UK).

Abbreviations: CAN, Canada; ESP, Spain, SWE, Sweden; SEK, Swedish krona; MIMS, monthly index of medical specialties; TLV, Tandvårds- och läkemedelsförmånsverket [dental and pharmaceutical benefits agency].

Table 5 Direct costs (€2014) by GOLD state and type of event

Event/GOLD	CAN ^{43,44}			ESP ^{45,46}			SWE ^{47,48}			UK ²⁶		
	II	III	IV	II	III	IV	II	III	IV	II	III	IV
No Ex	95	284	416	366	1,060	1,751	141	333	472	150	321	531
Non-SevEx	391	580	712	669	1,363	2,054	486	678	817	153	474	684
SevEx	7,108	7,297	7,428	1,822	2,516	3,207	3,058	3,250	3,389	4,832	5,153	5,363

Notes: Ex-rates 2014: CAN (C\$ to €: 0.68)⁴⁰; SWE (SEK to €: 0.11)⁴¹; UK (£ to €: 1.24).⁴² Where necessary, costs have been inflated to 2014 year prices and recalculated to reflect 3-month cycle.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOLD II, GOLD classification indicating moderate COPD; COPD, chronic obstructive pulmonary disease; GOLD III, GOLD classification indicating severe COPD; GOLD IV, GOLD classification indicating very severe COPD; CAN, Canada; ESP, Spain, SWE, Sweden; No Ex, no exacerbation; Non-SevEx, nonsevere exacerbation; SevEx, severe exacerbation; SEK, Swedish krona.

Results

Base case

Base case results are presented in Table 7. TIO added 0.21 (CAN), 0.25 (ESP), 0.23 (SWE), and 0.23 (UK) quality-adjusted life years (QALYs) compared to GLY over the lifetime of the average patient. The incremental costs (€2014) compared to GLY were –€623 (CAN), €1,066 (ESP), €264 (SWE), and –€169 (UK). Thus, in the case of UK and CAN, TIO was found to be cost saving, as it was both more effective and less costly than GLY. For ESP and SWE, the cost per QALY (incremental cost-effectiveness ratios [ICERs]) was positive but small, at €4,281 and €1,137, respectively. The estimated ICERs are well below the existing willingness-to-pay thresholds for ESP (€30,000) and SWE (–€50,000–€100,000).

Sensitivity analyses

Deterministic one-way sensitivity analyses were performed on key model parameters, in order to assess their impact on the main results.

Table 8 shows how the ICERs were affected when varying key model parameters one at a time. The scenarios that consistently impacted the ICER the most were a shorter time horizon and a lower RR of severe exacerbations. Shortening the time horizon to 5 years lowered the ICER. Lowering the

Table 6 Utility weights by GOLD state and type of exacerbation

Event/GOLD	CAN/UK			ESP			SWE		
	II	III	IV	II	III	IV	II	III	IV
No Ex	0.79	0.75	0.65	0.82	0.72	0.57	0.73	0.74	0.52
Non-SevEx	0.77	0.74	0.64	0.81	0.71	0.56	0.72	0.73	0.51
SevEx	0.74	0.70	0.61	0.78	0.69	0.54	0.69	0.70	0.49

Notes: Weights for mild and moderate exacerbations were merged (averaged) if necessary to form “nonsevere exacerbation”. Utility weights were derived using the EQ-5D questionnaire. Data from Hettle et al²⁶ (CAN/UK), Miravittles et al⁴⁹ (ESP), and Stahl et al⁵⁰ (SWE).

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOLD II, GOLD classification indicating moderate COPD; COPD, chronic obstructive pulmonary disease; GOLD III, GOLD classification indicating severe COPD; GOLD IV, GOLD classification indicating very severe COPD; CAN, Canada; ESP, Spain, SWE, Sweden; No Ex, no exacerbation; Non-SevEx, nonsevere exacerbation; SevEx, severe exacerbation; EQ-5D, Euroqol 5 dimension.

Table 7 Base case results

	Tiotropium	Glycopyrronium	Difference
CAN			
Costs (€)			
Treatment costs	1,933	1,554	380
Direct costs	20,171	21,174	-1,003
Total direct costs	22,105	22,728	-623
Health outcomes			
QALYs	6.75	6.54	0.21
Life years	9.00	8.72	0.28
ICER (€)			TIO dom
ESP			
Costs (€)			
Treatment costs	1,318	1,255	63
Direct costs	39,812	38,809	1,003
Total direct costs	41,129	40,063	1,066
Health outcomes			
QALYs	7.77	7.52	0.25
Life years	10.47	10.14	0.34
ICER (€)			4,281
SWE			
Costs (€)			
Treatment costs	1,898	1,532	366
Direct costs	18,171	18,273	-102
Total direct costs	20,069	19,805	264
Health outcomes			
QALYs	7.25	7.02	0.23
Life years	10.26	9.93	0.33
ICER (€)			1,137
UK			
Costs (€)			
Treatment costs	1,865	1,503	362
Direct costs	19,285	19,816	-531
Total direct costs	21,150	21,319	-169
Health outcomes			
QALYs	7.37	7.13	0.23
Life years	9.82	9.51	0.31
ICER (€)			TIO dom

Notes: Discount rates: all costs and effects are discounted at an annual rate of CAN, 5%; ESP, 3%; SWE, 3%; and UK, 3.5%.

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; CAN, Canada; ESP, Spain; SWE, Sweden; TIO dom, tiotropium dominating.

RR of severe exacerbations to the 95% lower limit found in SPARK (GLY/TIO RR SevEx: 1.05) increased the ICER by >€10,000 in CAN, SWE, and UK.

Figure 2 further explores the impact of the most important factor in explaining the results, the RR of severe exacerbations. When it is assumed that TIO and GLY are equally efficacious (RR SevEx: 1.00), TIO is dominated by GLY. This is a trivial result given that the two therapies are equally efficacious in every other regard and that GLY is less expensive. However, for CAN, SWE, and UK, as the RR increases in favor of TIO, the ICER quickly declines. For ESP, the decline is not as large, due to the smaller price difference between TIO and GLY in ESP (3% in ESP vs 22% in the other countries). Nevertheless, already at an RR of 1.02–1.03, TIO can be considered borderline cost-effective by most countries' willingness-to-pay

thresholds. At an RR of 1.43 (found in SPARK¹⁹), TIO would certainly be considered a cost-effective alternative to GLY.

Discussion

The primary objective of this study was to assess the cost-effectiveness of TIO monotherapy compared to GLY monotherapy in moderate to very severe COPD patients in CAN, ESP, SWE, and the UK. TIO was found to be cost-effective compared to GLY in all four countries. The results were to a large extent driven by the lower risk of severe exacerbations observed in the TIO cohort.

The SPARK estimate of relative efficacy of severe exacerbations (GLY/TIO RR SevEx: 1.43, $P=0.025$) is high compared to existing reviews and network meta-analyses of bronchodilators in COPD.^{28,51} These studies do not find any

Table 8 One-way sensitivity analysis (ICER €2014)

Variable of interest	Input	CAN	ESP	SWE	UK
Base case		TIO dom	4,281	1,137	TIO dom
Discount rates	Costs: 0%, effects: 0%	TIO dom	4,505	1,442	81
	Costs: 6%, effects: 6%	TIO dom	4,039	814	TIO dom
	Costs: 6%, effects: 0%	TIO dom	2,328	475	TIO dom
Time horizon	5 years	TIO dom	1,174	TIO	TIO dom
	10 years	TIO dom	3,617	227	TIO dom
	20 years	TIO dom	4,212	1,047	TIO dom
Treatment duration	1 year	TIO dom	4,147	1,070	TIO dom
	10 years	TIO dom	4,458	1,316	TIO dom
	Life (35 years)	TIO dom	4,707	1,631	TIO dom
Sex	Males only	TIO dom	4,174	1,048	TIO dom
	Females only	TIO dom	4,364	1,213	TIO dom
Start age	40 years	TIO dom	3,504	216	TIO dom
	80 years	2,293	4,384	1,201	TIO dom
GOLD start distribution	All start in GOLD II	TIO dom	4,136	1,402	TIO dom
	All start in GOLD III	TIO dom	4,318	997	TIO dom
	All start in GOLD IV	TIO dom	4,661	770	TIO dom
Subgroup	GOLD II	TIO dom	1,421	1,276	TIO dom
	GOLD III	TIO dom	5,259	1,087	TIO dom
	GOLD IV	TIO dom	11,421	2,112	TIO dom
Mortality	GOLD state mortality = normal mortality (not adjusted for COPD)	TIO dom	4,384	1,255	TIO dom
	20% higher excess mortality (SevEx)	TIO dom	4,440	1,355	TIO dom
	20% lower excess mortality (SevEx)	TIO dom	4,088	876	TIO dom
Effect of tiotropium on SevEx	Low 95% CI from SPARK ³ (RR SevEx: 1.05)	9,942	5,875	12,509	10,102
	High 95% CI from SPARK ³ (RR SevEx: 1.97)	TIO dom	4,161	308	TIO dom
	RR SevEx: 1.00 for GOLD II patients	TIO dom	4,579	1,691	TIO dom
Direct costs of SevEx	20% higher	TIO dom	3,909	611	TIO dom
	20% lower	TIO dom	4,592	1,576	TIO dom
QoL loss of SevEx exacerbations	0% loss	TIO dom	4,309	1,145	TIO dom
	20% loss	TIO dom	4,195	1,113	TIO dom

Notes: *Base case: RR SevEx GLY versus TIO = 1.43.

Abbreviations: ICER, incremental cost-effectiveness ratio; CAN, Canada; ESP, Spain; SWE, Sweden; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GOLD II, GOLD classification indicating moderate COPD; GOLD III, GOLD classification indicating severe COPD; GOLD IV, GOLD classification indicating very severe COPD; COPD, chronic obstructive pulmonary disease; SevEx, severe exacerbation; CI, confidence interval; RR, relative risk; QoL, quality of life; TIO dom, tiotropium dominating; GLY dom, glycopyrronium dominating; TIO, tiotropium; GLY, glycopyrronium.

large and significant difference between LAMAs (eg, TIO, GLY, and aclidinium) either when it comes to effect on lung function or exacerbations.^{28,51} However, there are still inherent problems with comparing trials that have differing designs, that allow different co-treatments, and that have varying length of follow-up.⁵² These problems will be important when comparing exacerbation outcomes indirectly. Comparing SPARK to other relevant trials (eg, GLOW2²⁷), SPARK had longer follow-up, was more favorably designed to detect moderate to severe exacerbations, and included more severe patients. This likely affected the ability to detect and record severe events.

Exacerbation prevention is an important goal in the management of COPD and that cost-effectiveness is highly dependent on the ability to prevent exacerbations, particularly severe ones that lead to costly hospitalizations. This study has shown that given the best available head-to-head evidence on exacerbations to date (SPARK), the balance would likely

sway in favor of TIO being a cost-effective alternative to GLY. In fact, our findings suggest that a much lower RR of severe exacerbations than the one found in SPARK would suffice to render TIO a cost-effective intervention compared to GLY.

The results presented here compare two dry powder inhalers (Spiriva HandiHaler and Seebri Breezhaler). TIO can also be delivered using the Respimat® inhaler, a soft mist inhaler (inhalation spray). The Tiotropium Safety and Performance in Respimat (TIO SPIR) trial showed that Respimat had a safety profile and exacerbation efficacy similar to that of the HandiHaler device.⁵³ In addition, a head-to-head in vitro dose comparison between Respimat and Breezhaler found that Respimat delivered significantly higher doses of the drug to the lung (Respimat: 60–70 [% not determined]; Breezhaler 50–60 [% not determined]).⁵⁴ These findings suggest that Respimat can successfully deliver TIO with maintained efficacy and safety and with far less drug deposition in the upper throat. In light of these

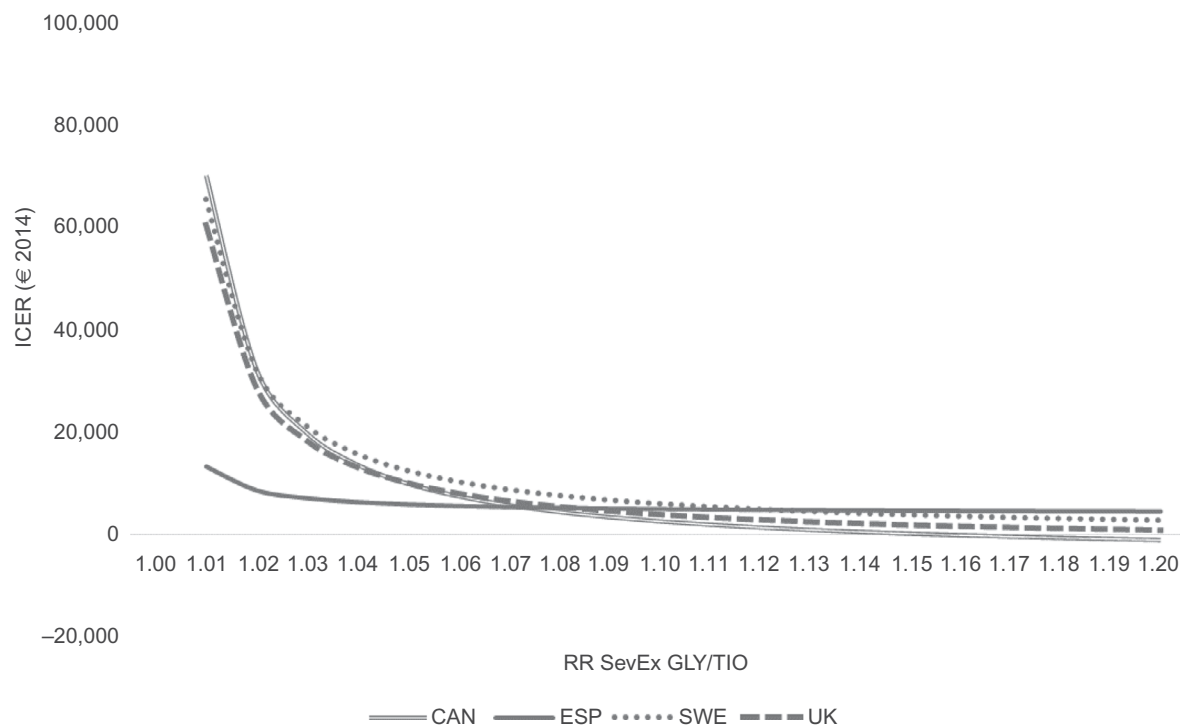


Figure 2 Impact of RR SevEx on ICER.

Abbreviations: RR, relative risk; SevEx, severe exacerbation; ICER, incremental cost-effectiveness ratio; GLY, glycopyrronium; TIO, tiotropium; CAN, Canada; ESP, Spain; SWE, Sweden.

findings, we expect the cost-effectiveness results to be applicable also to cases where TIO is delivered via the Respimat device.

Extensive sensitivity analyses were conducted to assess the impact of key parameters on the main results. The relative efficacy of the interventions, particularly in preventing severe exacerbations, played an important role in explaining cost-effectiveness. In this regard, it is important to remember the basic design and purpose of the UPLIFT and SPARK trials and how these factors potentially affected the results. The purpose of the UPLIFT trial was to assess the effect of the interventions on overall lung function; exacerbations were only a secondary objective. Additionally, the patients received usual non-LAMA care in both arms. This included LABA and/or corticosteroid therapy in a majority of the patients enrolled. The trial, not being primarily designed to detect exacerbations and the use of alternative inhaled therapy, likely pushed rates of exacerbations downward. This may explain why the study found no significant difference in the rates of severe exacerbations between the two arms.

As opposed to the UPLIFT trial, the SPARK trial was designed specifically to detect moderate and severe exacerbations.^{16,19} High-risk patients, that is, those having had at least one moderate exacerbation in the past year, were enrolled and randomly assigned to receive either QVA149 (LABA/LABA combination), TIO, or GLY. Importantly, patients who

were receiving LABA therapy discontinued the therapy upon enrolling in the trial, although ICS therapy continued. Indeed, these circumstances suggest that the SPARK trial was more favorably designed to detect and record exacerbations. Having said that, there were only 364 severe exacerbations reported in total across all three arms in SPARK. The low number of observed severe exacerbations naturally introduces some uncertainty in the estimate of the RR between TIO and GLY. It is important to keep in mind that, as opposed to mild and moderate exacerbations, severe exacerbations are infrequent events in COPD. In addition, SPARK did not include a placebo arm, which means that all arms in the trial contained active therapy with the specific aim of lowering rates of exacerbations.¹⁹ These circumstances suggest that even if a trial is favorably designed to detect severe exacerbations, it is always going to be difficult to amass a large study population to record many severe exacerbations. Future research should continue to focus efforts on disentangling the relative efficacy of different types of bronchodilators in preventing these rare events, as they are important factors explaining morbidity, mortality, and cost-effectiveness in COPD.

A potential drawback with this study, like any other utilizing trial data, is that the patient population might be somewhat different from the actual population of COPD patients (GOLD II–IV). Measures were taken to limit this potential bias, eg, by

applying country-specific mortality rates. Furthermore, one should interpret differences between countries with caution, as there are substantial differences in the organization of health care and its funding. Differences in the way unit costs are estimated may also play an important role. Finally, it is important to keep in mind that the model presented here evaluates an exploratory scenario where the two cohorts are equal in every other regard except in terms of the risk of experiencing exacerbation.

Conclusion

Clinical data from UPLIFT and SPARK studies were incorporated in a Markov cohort model, which explicitly modeled the effects of exacerbations. Cost-effectiveness of TIO was assessed relative to GLY. TIO was found to be cost-effective relative to GLY given the current state of clinical evidence. The findings were to a large extent driven by TIO being relatively efficacious in preventing severe exacerbations, based on the findings in the SPARK trial.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The study was sponsored by Boehringer Ingelheim (a manufacturer of Spiriva [tiotropium]). OE and FB independently designed and executed the study. FA, JF, AT, MEO, CC, and MB are employees of Boehringer Ingelheim. The authors report no other conflicts of interest in this work.

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