Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation

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ABSTRACT Ivacaftor, a breakthrough treatment for cystic fibrosis (CF) patients with the G551D genetic mutation, lacks long-term clinical and cost projections. This study forecasted outcomes and cost by comparing ivacaftor plus usual care *versus* usual care alone.

A lifetime Markov model was conducted from a US payer perspective. The model consisted of five health states: 1) forced expiratory volume in 1 s (FEV_1) % pred ⩾70%, 2) 40%⩽ FEV_1 % pred <70%, 3) FEV_1 % pred <40%, 4) lung transplantation and 5) death. All inputs were extracted from published literature. Budget impact was also estimated. We estimated ivacaftor's improvement in outcomes compared with a non-CF referent population.

Ivacaftor was associated with 18.25 (95% credible interval (CrI) 13.71–22.20) additional life-years and 15.03 (95% CrI 11.13–18.73) additional quality-adjusted life-years (QALYs). Ivacaftor was associated with improvements in survival and QALYs equivalent to 68% and 56%, respectively, for the survival and QALY gaps between CF usual care and their non-CF peers. The incremental lifetime cost was $3 374 584. The budget impact was $0.087 per member per month.

Ivacaftor increased life-years and QALYs in CF patients with the G551D mutation, and moved morbidity and mortality closer to that of their non-CF peers. Ivacaftor costs much more than usual care, but comes at a relatively limited budget impact.

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Received: Aug 30 2015 | Accepted after revision: March 05 2016 | First published online: April 28 2016

Conflict of interest: None declared.

Introduction

Cystic fibrosis (CF) is one of the most common lifelong genetic diseases with approximately 30 000 patients in the USA [1]. CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene [2]. Alteration of *CFTR* results in a variety of clinical manifestations, including lung and pancreatic secretion abnormalities. There are around 1900 disease-causing alleles and G551D represents ~5%, while non-G551D gating represents ~6% [3, 4].

Ivacaftor is the first of a new breakthrough class of medications called CFTR potentiators. Recent randomised controlled clinical trials (RCTs) show that ivacaftor improves lung function assessed by forced expiratory volume in 1 s (FEV_1) % pred in CF patients with mild to moderate lung disease [5, 6]. Moreover, several studies report the improvement of lung function among CF patients with severe lung disease who received ivacaftor [7–11]. Ivacaftor has been approved by the US Food and Drug Administration (FDA) for CF patients aged at least 6 years who have including G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R mutations of the *CFTR* gene [12]. However, because the prevalence of the G551D mutation represents the vast majority of US CF patients as compared with the other FDA-approved *CFTR* mutations for ivacaftor, this study focused on only CF patients with the G551D mutation.

Previous ivacaftor RCTs [5, 6, 13] showed improvement of lung function over an observation period of 96 weeks. Although lung function improvement is an important marker of CF, long-term treatment with ivacaftor has not been studied related to its possible impact on mortality, health-related quality of life or the probability of lung transplantation. Moreover, because ivacaftor is a high-cost treatment [14], the impact of ivacaftor on lifetime cost and its budget impact on the US population are important for decision makers when considering coverage and reimbursement. The UK has estimated the long-run value of ivacaftor based on decision-analytic models [15]; however, to the best of our knowledge, similar modelling methods have not been used to estimate the US-related value of ivacaftor. Therefore, our primary objective was to forecast lifetime outcomes and cost to compare ivacaftor plus usual care *versus* usual care alone in CF patients who carry the G551D mutation from the US payer perspective. In addition, we compared the long-run projected clinical impact of ivacaftor to a non-CF referent US population.

This study was presented as an abstract at the 20th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Philadelphia, PA, USA (May 16–20, 2015).

Methods

Model description

A Markov model was created to forecast the average lifetime cost per patient, average life expectancy, quality-adjusted life-years (QALYs) and probability of lung transplantation of two treatment options: 1) ivacaftor 150 mg twice daily plus usual care and 2) usual care alone. CF usual care consisted of pancreatic enzymes, periodic intravenous antibiotics and dornase alpha (DNase) as studied within their pivotal RCTs [5, 6, 13]. A hypothetical cohort of 1000 CF patients with the G551D mutation, starting at 25 years of age, was simulated. In addition, we forecasted the lifetime average life expectancy and QALYs for the non-CF average US population. 25 years was selected based on the average age of CF patients with the G551D mutation in a pivotal clinical trial [6]. The model consisted of three lung-function-defined health states, *i.e.* mild lung disease (FEV_1 % pred $\geqslant$70%), moderate lung disease (40%$\leqslant$ FEV_1 % pred <70%) and severe lung disease (FEV_1 % pred <40%), along with health states representing lung transplantation and death (figure 1).

The percentages of patients entering the model's lung function health states were 72%, 21% and 7% for mild, moderate and severe lung disease, respectively [1]. Each patient could remain in the same state or progress to more severe states. If a patient with usual care alone progressed to more severe states, he/she could remain in that state or progress to a more severe health state, lung transplantation or death. He/she could not move to less severe states. However, patients treated with ivacaftor could move to less severe states, remain in the same state or progress to more severe states. Once a patient progressed to lung transplantation, he/she could not move back to FEV_1 % pred states. We estimated the impact of ivacaftor under a US healthcare payer perspective using a cycle length of 1 year with a lifetime horizon.

Model inputs and assumptions

Literature reviews informed model inputs (table 1). The probability of FEV_1 % pred decline as well as the probability of receiving a lung transplant [16] were applied for both treatment comparators. The probabilities of moving from moderate to mild and severe to moderate lung disease for the ivacaftor arm were derived from previous RCTs [5, 6]. As the efficacy of ivacaftor was reported as an absolute increase in FEV_1 % pred, Monte Carlo simulations were performed to estimate the likelihood of moving from moderate to mild and severe to moderate lung disease. The Monte Carlo simulations estimated the FEV_1 % pred distribution within the moderate and severe lung disease health states. The estimated FEV_1 % pred values were added to the absolute increase in FEV_1 % pred from the ivacaftor RCTs. The average FEV_1 %

 DOI: 10.1183/13993003.01444-2015

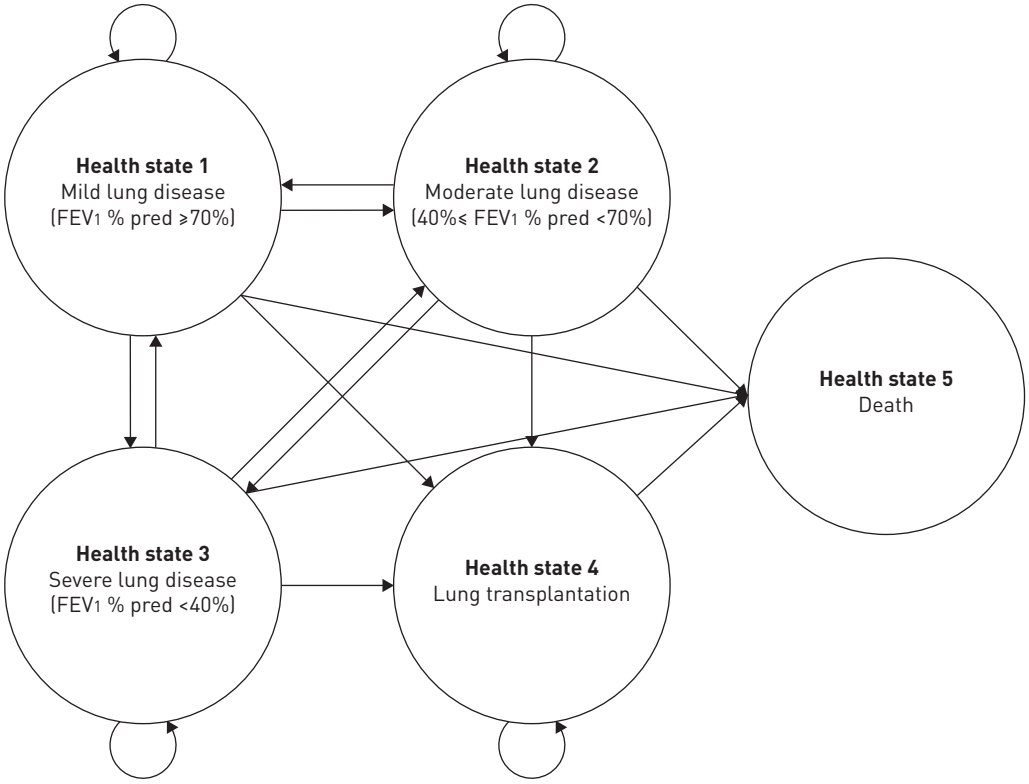

FIGURE 1 A Markov model for ivacaftor in patients with cystic fibrosis. FEV_1: forced expiratory volume in 1 s.

pred for the Monte Carlo simulation was assumed as 55.0±5.0% for moderate lung disease and 30.0±5.0% for severe lung disease.

Consistent with the ivacaftor efficacy RCTs [5, 6, 13], patients were allowed to continue their pre-study medications except for hypertonic saline which was not approved in the USA. We assumed the use of usual care medications was balanced across the RCT arms and therefore the cost of usual care would not impact the incremental cost or outcome results.

Mortality risk for mild lung disease was assumed to be equal to the non-CF population [17], while the mortality risks for moderate, severe lung disease and lung transplantation were based on previous studies [18, 19]. QALYs were calculated based on the life expectancy and utilities for each of the health states, which were based on a previous study [15].

All costs were expressed in 2013 US$ and discounted at an annual rate of 3.0% [20], while the outcomes were not discounted because we wanted to estimate the overall clinical impact of ivacaftor rather than the incremental present value for money. The undiscounted outcomes, therefore, represent the forecasted clinical impact of ivacaftor. Costs and healthcare resource utilisation for each health state were based on previous studies [21–24], and are reported in table 1. Ivacaftor cost was derived from the US wholesale acquisition price, which was $426.72 per tablet [14]. As the patent of ivacaftor will expire in May 2027, we assumed the cost of ivacaftor after patent expiration as 10% of the current price.

Analyses

Outcomes of interest were life expectancy, QALYs, probability of having a lung transplant and lifetime costs. Assuming a generic representative payer and population of 1 million US lives, the budget impact analysis was performed based on the first 3, 5 and 10 years of direct costs. Base-case analysis was performed based on the assumption that the efficacy of ivacaftor after 2 years was 50% of the efficacy shown in the RCTs [5, 6, 13]. This is considered a relatively conservative assumption related to ivacaftor's potential long-run benefit and was similar to the UK's assumption related to the long-run efficacy of ivacaftor [15]. Additional scenario analyses were performed by varying the assumption of efficacy of ivacaftor after 2 years and starting age of the cohort (table 2). We considered starting ages of 6, 9 and 12 years as scenario analyses because 6 and 12 years were the starting ages while 9 years was the average age of pivotal clinical studies [5, 6]. The effect of uncertainty in the input parameters was explored using one-way sensitivity analysis. Probabilistic sensitivity analysis was also performed using Monte Carlo

TABLE 1 Model inputs

	Base-case value (range)	Distribution	Reference
Efficacy of ivacaftor			
Patient			
Aged 6–11 years	10.0 (–)		[5]
Aged ⩾12 years	10.5 (–)		[6]
Relative risk of pulmonary exacerbation			
Aged 6–11 years	1.0 (–)		[5]
Aged ⩾12 years	0.43 (0.27–0.59)	Log-normal	[6]
Relative risk of pulmonary exacerbation hospitalisation			
Aged 6–11 years	1.0 (–)		[5]
Aged ⩾12 years	0.64 (0.40–1.00)	Log-normal	[6]
Average FEV_1 % pred for moderate lung disease			
Aged 6–11 years	30.0 (20.20–39.80)	Gamma	Assumption
Aged ⩾12 years	55.0 (45.20–64.80)	Normal	Assumption
Transition probability			
Mild to moderate lung disease	Vary based on age (–)	Beta	[16]
Mild to severe lung disease	Vary based on age (–)	Beta	[16]
Mild to lung transplantation	Vary based on age (–)	Beta	[16]
Moderate to severe lung disease	Vary based on age (–)	Beta	[16]
Moderate to lung transplantation	Vary based on age (–)	Beta	[16]
Severe lung disease to lung transplantation	Vary based on age (–)	Beta	[16]
Mortality data			
Mild lung disease to death	Age-specific mortality (–)		[17]
Moderate lung disease to death	0.030 (0.025–0.375)	Uniform (±25%)	[18]
Severe lung disease to death	0.070 (0.053–0.088)	Uniform (±25%)	[18]
Lung transplantation to death	0.152 (0.139–0.165)	Beta	[19]
Healthcare resource utilisation			
Mild lung disease			
Hospitalisation	0.20 (0–0.894)	Gamma	[21]
Outpatient hospitalisation	0.10 (0–0.447)	Gamma	[21]
Clinic visits	7.00 (0–16.690)	Gamma	[21]
Probability of patients using pancreatic enzymes	0.89 (–)		[21]
Probability of patients using intravenous antibiotics	0.02 (–)		[21]
Probability of patients using DNase	0.36 (–)		[21]
Moderate lung disease			
Hospitalisation	0.40 (0–1.488)	Gamma	[21]
Outpatient hospitalisation	0.30 (0–1.541)	Gamma	[21]
Clinic visits	7.00 (0–15.790)	Gamma	[21]
Probability of patients using pancreatic enzymes	0.84 (–)		[21]
Probability of patients using intravenous antibiotics	0.49 (–)		[21]
Probability of patients using DNase	0.72 (–)		[21]
Severe lung disease			
Hospitalisation	1.70 (0–4.399)	Gamma	[21]
Outpatient hospitalisation	1.40 (0–5.058)	Gamma	[21]
Clinic visits	10.00 (0–22.100)	Gamma	[21]
Probability of patients using pancreatic enzymes	0.95 (–)		[21]
Probability of patients using intravenous antibiotics	0.71 (–)		[21]
Probability of patients using DNase	0.71 (–)		[21]
Probability of double lung transplantation	0.964 (0.960–0.968)	Beta	[24]
Cost US$			
Mild lung disease			
Hospitalisation	2406.61 (0–18522.86)	Gamma	[21]
Clinic visit	2406.61 (0–6730.48)	Gamma	[21]
DNase	3008.26 (0–13228.32)	Gamma	[21]
Outpatient antibiotics	802.20 (0–3946.84)	Gamma	[21]
Pancreatic enzymes	3008.26 (0–8904.45)	Gamma	[21]
Other medications	1002.75 (0–3361.23)	Gamma	[21]
Moderate lung disease			
Hospitalisation	7821.47 (0–60101.04)	Gamma	[21]
Clinic visit	2206.06 (0–8310.82)	Gamma	[21]
DNase	5214.32 (0–20568.48)	Gamma	[21]
Outpatient antibiotics	1604.41 (0–13613.38)	Gamma	[21]

Continued

DOI: 10.1183/13993003.01444-2015

TABLE 1 Continued

	Base-case value (range)	Distribution	Reference
Pancreatic enzymes	3008.26 (0–7909.72)	Gamma	[21]
Other medications	1203.30 (0–2374.52)	Gamma	[21]
Severe lung disease			
Hospitalisation	56 154.20 (0–224 392.18)	Gamma	[21]
Clinic visit	6217.07 (0–17 616.37)	Gamma	[21]
DNase	10 027.54 (0–31 646.90)	Gamma	[21]
Outpatient antibiotics	9425.88 (0–53 843.85)	Gamma	[21]
Pancreatic enzymes	2406.61 (0–7516.64)	Gamma	[21]
Other medications	2807.71 (0–13 420.85)	Gamma	[21]
Single lung			
30 days pre-transplant	10 889.39 (8167.05–13 611.74)	Uniform (±25%)	[22]
Procurement	77 283.01 (57 962.26–96 603.76)	Uniform (±25%)	[22]
Hospital transplant admission	320 232.87 (240 174.66–400 291.09)	Uniform (±25%)	[22]
Physician fee during transplantation	35 416.97 (26 562.73–44 271.22)	Uniform (±25%)	[22]
180 days post-transplantation	124 435.16 (93 326.37–155 543.95)	Uniform (±25%)	[22]
Outpatient immunosuppressant and other medication	25 056.19 (18 792.14–31 320.23)	Uniform (±25%)	[22]
Follow-up in months 7–12 after transplantation	65 459.75 (49 094.81–81 824.69)	Uniform (±25%)	[23]
Follow-up for the following year	108 899.04 (81 674.28–136 123.80)	Uniform (±25%)	[23]
Double lung			
30 days pre-transplant	22 624.57 (16 968.43–28 280.72)	Uniform (±25%)	[22]
Procurement	95 467.25 (71 600.43–119 334.06)	Uniform (±25%)	[22]
Hospital transplant admission	484 736.79 (363 522.59–605 920.98)	Uniform (±25%)	[22]
Physician fee during transplantation	59 521.67 (44 641.25–74 402.08)	Uniform (±25%)	[22]
180 days post-transplantation	150 760.01 (113 070.01–188 450.02)	Uniform (±25%)	[22]
Out-patient immunosuppressant and other medication	29 813.69 (22 360.27–37 267.11)	Uniform (±25%)	[22]
Follow-up in months 7–12 after transplantation	65 459.75 (49 094.81–81 824.69)	Uniform (±25%)	[23]
Follow-up for the following year	108 899.04 (81 674.28–136 123.80)	Uniform (±25%)	[23]
Ivacaftor per tablet	426.72 (320.04–533.40)	Uniform (±25%)	[14]
Utility			
Patients with mild lung disease	0.803 (0.752–0.854)	Beta	[15]
Patients with moderate lung disease	0.749 (0.708–0.790)	Beta	[15]
Patients with severe lung disease	0.688 (0.639–0.737)	Beta	[15]
Patients with lung transplantation	0.810 (0.732–0.888)	Beta	[15]

FEV1: forced expiratory volume in 1 s.

simulations with 1000 iterations and presented as the 95% credible interval (CrI) of each outcome (2.5 and 97.5 percentile). Uncertainty in model inputs was derived from 95% confidence intervals from the literature where such evidence existed.

We also compared life expectancy and QALY of patients receiving ivacaftor plus usual care or usual care alone with the non-CF population. The survival data of the non-CF population was from US life tables [17], while average utility which was used to estimate QALYs for the average non-CF population was obtained from a previous US survey [25].

Results

Main results

Ivacaftor was associated with an 18.27% (95% CrI 13.63–22.85) absolute decrease in the likelihood of experiencing a lung transplant, an average of 18.25 (95% CrI 13.71–22.20) additional life-years, 15.03 (95% CrI 11.13–18.73) additional QALYs and $3 374 584 (95% CrI 1 651 192–4 634 390) incremental lifetime cost (table 3).

Effect of input uncertainty

One-way sensitivity analysis indicated that uncertainty on several important inputs would affect the incremental life expectancy and QALYs. They included average FEV1 % pred for moderate lung disease in patients, efficacy of ivacaftor for patients aged ⩾12 years, average FEV1 % pred for severe lung disease, utility for mild lung disease and mortality rate associated with moderate lung disease (figure 2).

For the effect of uncertainty of inputs on incremental cost, the most important factor was cost of ivacaftor. Other uncertainty in inputs which affected incremental cost included mortality of severe lung disease,

TABLE 2 Description of scenario analyses

Number	Scenario	Starting age years	Description	Treatment duration
1	Base-case	25	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, there is 50% efficacy of ivacaftor	Lifetime
2	Optimistic	25	There is full efficacy of ivacaftor though lifetime horizon	Lifetime
3	Intermediate	25	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, there is 66% efficacy of ivacaftor	Lifetime
4	Conservative	25	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, patients stop the treatment	2 years
5	6-year-old	6	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, there is 50% efficacy of ivacaftor; the starting age of the cohort is 6 years	Lifetime
6	9-year-old	9	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, there is 50% efficacy of ivacaftor; the starting age of the cohort is 9 years	Lifetime
7	12-year-old	12	There is full efficacy of ivacaftor within first 2 years of treatment; after 2 years, there is 50% efficacy of ivacaftor; the starting age of the cohort is 12 years	Lifetime

hospitalisation cost of severe lung disease, number of hospitalisations per year of severe lung disease and clinical visit cost of mild or severe lung disease.

Scenario analyses

By ranging efficacy after 2 years

Scenario analyses for lifetime treatment indicated that ivacaftor treatment was associated with additional life-years ranging from 19.23 to 30.59 years, while it was associated with additional QALYs ranging from 15.85 to 25.64 QALYs. The incremental lifetime costs ranged from $3 388 927 to $3 540 660 (table 4).

By ranging starting age of cohort

Scenario analyses for varying the starting age of the hypothetical cohorts indicated that ivacaftor was associated with additional life-years ranging from 18.09 to 19.56 years, while it was associated with additional QALYs ranging from 14.92 to 16.03 QALYs. The incremental lifetime costs ranged from $3 455 593 to $3 740 480 (table 4).

Comparison with non-CF population

Based on the estimated average life expectancy for the non-CF population (approximately 49.47 years), ivacaftor plus usual care (average survival of 41.04 years) was associated with closing the survival gap between usual care CF (22.78 years) and their non-CF peers (49.47 years) by approximately 68%. Similarly, ivacaftor plus usual care (average 32.18 QALYs) was associated with closing the QALY gap between usual care CF (17.15 QALYs) and their non-CF peers (43.85 QALYs) by approximately 56% (figure 3).

Budget impact analysis

The budget impact analysis indicated that ivacaftor was associated with about $0.087 (95% CrI 0.064–0.111) per member per month for a 3-year time horizon, and $0.083 (95% CrI 0.059–0.106) and $0.074 (95% CrI 0.052–0.095) for the first 5 and 10 years, respectively.

TABLE 3 Results of base-case analysis

	Usual care	Ivacaftor plus usual care	Incremental value[#]
Receiving lung transplantation %	30.27 (27.26–34.31)	12.00 (8.87–16.18)	−18.27 (−22.85– −13.63)
Estimated life expectancy years	47.78 (46.66–49.21)	66.04 (61.35–70.11)	18.25 (13.71–22.20)
Estimated quality-adjusted life-years	42.15 (41.15–43.37)	57.18 (53.02–61.19)	15.03 (11.13–18.73)
Estimated lifetime cost US$	1 130 184 (461 764–3 435 325)	4 504 768 (3 442 654–5 892 376)	3 374 584 (1 651 192–4 634 390)

Data are presented as n (95% credible interval). All findings estimated based on the 25-year-old starting cohort. [#]: ivacaftor plus usual care *versus* usual care alone.

DOI: 10.1183/13993003.01444-2015

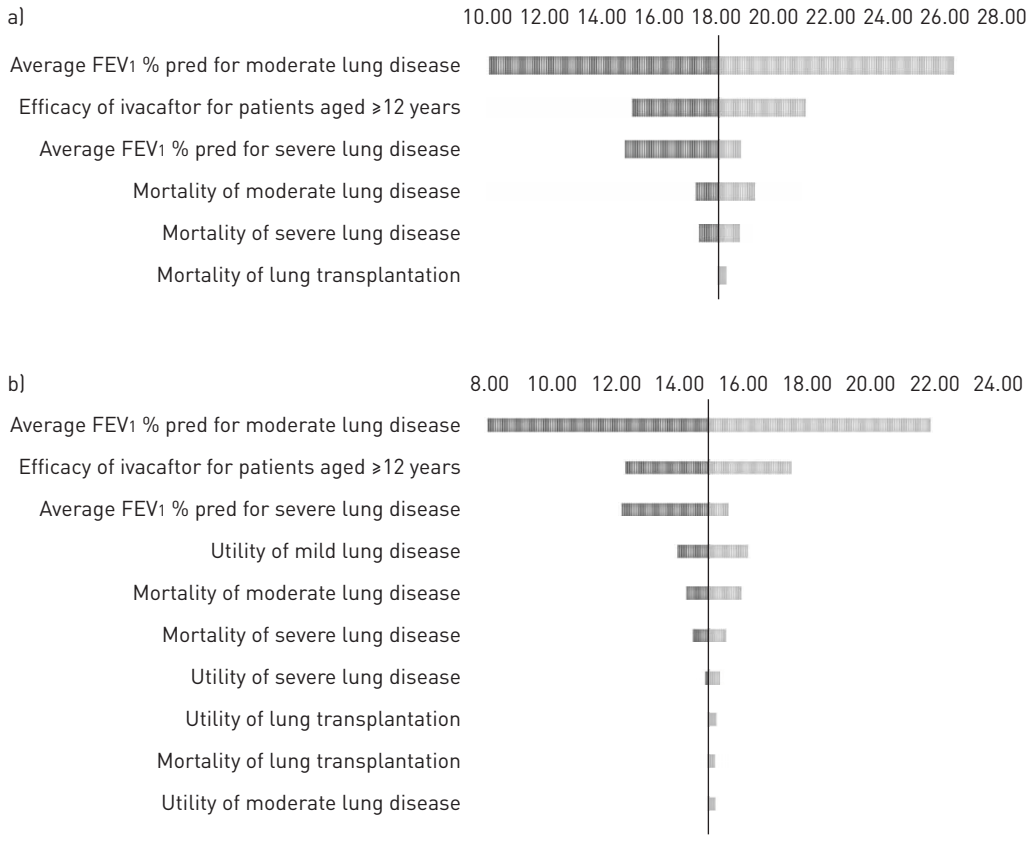

FIGURE 2 One-way uncertainty of inputs on a) incremental life expectancy and b) incremental quality-adjusted life-year. FEV_1: forced expiratory volume in 1 s.

Discussion

Our findings indicated that the use of ivacaftor added on to usual care increases life expectancy and QALYs in CF patients with the G551D mutation as compared with usual care. However, ivacaftor comes with much higher lifetime cost. Moreover, the findings were highly sensitive to the uncertainty of selected inputs and assumptions. The findings may be used by healthcare providers to discuss the possible long-run benefits of ivacaftor, and for decision makers to consider how to incorporate ivacaftor in their coverage and reimbursement policies.

To the best of our knowledge, this is the first study forecasting lifetime outcomes and costs of ivacaftor in the USA. A previous study [15] in the UK reported that ivacaftor increased 6.20 discounted life-years with 5.26 discounted QALYs assuming that the efficacy of ivacaftor after 90 weeks is the same as the efficacy within the first 90 weeks [15]. Those findings are not largely different from our model's optimistic scenario, which were 6.11 discounted incremental life-years or 5.21 discounted incremental QALYs.

In this study, we did not use a discounting approach for the clinical outcomes because the aim was to forecast the clinical impact of ivacaftor over a lifetime. Using discounted QALYs at the same 3% annual

TABLE 4 Results of scenario analysis

Scenario	Incremental absolute percentage of receiving lung transplantation	Additional life expectancy years	Additional quality-adjusted life-years	Incremental lifetime costs US$
Optimistic	−29.53 (−26.44–−33.38)	30.59 (27.31–33.68)	25.64 (21.79–29.12)	3 540 660 (1 310 481–5 507 336)
Intermediate	−19.01 (−14.98–−23.01)	19.23 (15.15–22.54)	15.85 (12.37–18.93)	3 388 927 (1 451 385–4 817 945)
Conservative	−1.16 (−0.79–−1.59)	1.16 (0.91–1.49)	0.91 (0.71–1.18)	443 814 (−511 469–727 012)
6-year-old	−18.50 (−22.05–−14.82)	18.09 (14.63–21.13)	14.92 (11.92–17.95)	3 740 480 (2 199 261–4 915 629)
9-year-old	−19.74 (−15.91–−23.59)	19.30 (15.39–22.60)	15.83 (12.27–19.19)	3 517 034 (1 936 263–4 716 440)
12-year-old	−20.04 (−15.72–−23.91)	19.56 (14.87–23.56)	16.03 (12.03–19.57)	3 455 593 (1 715 960–4 680 515)

Data are presented as n (95% credible interval), ivacaftor plus usual care *versus* usual care alone.

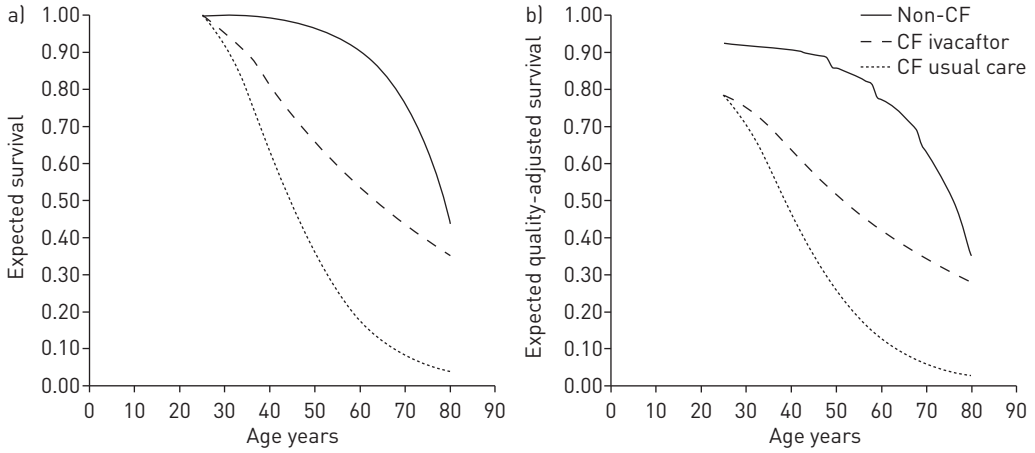

FIGURE 3 a) Expected survival and b) expected quality-adjusted survival given age comparing cystic fibrosis (CF) patients with the non-CF population.

rate as costs, the incremental QALYs were 5.21 (95% CrI 4.10–6.29) and the base-case incremental cost–effectiveness ratio was $648 230 (95% CrI 402 902–728 723) per QALY. We also estimated the lifetime costs and found that the lifetime costs of ivacaftor is about $3.4 million higher than usual care alone. However, the budget impact analysis indicated $0.088 per member per year, which may be tolerated by some US payers. CF is a rare disease that affects about 30 000 patients in the USA, whereas CF patients with the G551D mutation make up a small subset of this (approximately 1300 patients). Thus, policy makers should carefully consider all of the clinical and economic evidence in making coverage and reimbursement decisions for their insured populations even with the lifetime costs per treated patient being high.

We observed that the likelihood of lung transplantation is higher in patients with usual care than in patients with ivacaftor. This is due to patients receiving ivacaftor likely remaining in less severe lung disease than patients receiving usual care. The likelihood of lung transplantation is lower in patients with less severe lung disease. Thus, patients treated with ivacaftor were less likely to receive lung transplantation than patients with usual care.

Even though ivacaftor was recently approved and marketed in 2012, another CFTR-related medication called lumacaftor has also been recently approved and marketed. The combination of ivacaftor and lumacaftor will be used for CF patients with the F508del mutation. Findings from global phase III clinical trials indicate that the combination could improve FEV_1 % pred by about 2.4–4.0% compared with placebo. The combination also reduced the rate of pulmonary exacerbation about 30–39% [26]. Even at similar pricing to ivacaftor, this combination would have a massive impact on a health plan budget because of the higher prevalence of the F508del mutation. The Cystic Fibrosis Foundation reports that the prevalence of CF patients with the F508del mutation is about 86.7% of the total US CF patients [1] and the estimated percentage of patients homozygous for F508del is about 50%. Thus, the number of CF patients who will be eligible for this combination is about 43.4% of the total US CF patients. Based on the average wholesale price of the combination of ivacaftor and lumacaftor (approximately $854 per day) with an assumption of a similar clinical effect between ivacaftor alone and the combination, the projected budget impact is $0.884 per member per month or approximately $3.4 billion per year (given 100% assumed uptake). The projected budget impacts are $0.177, $0.353, $0.530 and $0.707 per member per month when assuming uptake percentages of 20%, 40%, 60% and 80%, respectively.

Several limitations in this study should be addressed. All inputs were based on existing literature. Findings from cost of care inputs were from dated literature [21]. Even though we converted the 1996 costs to present value using the medical consumer price index, the costs might differ from current actual costs. Standard of care transition probabilities were from an Australian study [16]. These probabilities might be different from that of the CF population in the US because of differences in patient care and the healthcare system. However, the study is the most recent study with a structure relevant to our model that reports transition probabilities. We believe that the transition probabilities from the Australian source are the best available evidence for use in our study. We also addressed the uncertainty of inputs by performing one-way and probabilistic sensitivity analyses. Future studies on specific inputs using appropriate study designs, large samples and accurate databases are needed to further reduce uncertainty.

This model was based on the 2-year observed efficacy of ivacaftor. The efficacy after 2 years was forecasted through various assumptions. In our base-case analysis, we assumed that the efficacy of ivacaftor was half

 DOI: 10.1183/13993003.01444-2015

of what was observed within the first 2 years because patients with chronic disease (such as CF) who need to take medications for a lifetime often have adherence challenges or other factors that may influence sustained response. Therefore, we assumed that the long-run effectiveness of ivacaftor may be reduced to half of the observed short-run efficacy. We further performed scenario analyses by varying the assumption of lung function benefit of ivacaftor after 2 years.

We assumed the cost of ivacaftor would decrease to 10% of the current price after the patent expires. Even if there was generic ivacaftor in the market, the price might not be as low as we assumed. However, our assumption was similar to the UK study [15].

Conclusion

Ivacaftor was associated with increases in life expectancy and QALYs in CF patients with the G551D mutation, and moved morbidity and mortality outcomes closer to that of their non-CF peers. The overall cost in patients with ivacaftor is much higher than usual care, but comes at a relatively limited budget impact. Uncertainty in this literature-informed analysis could be reduced with further observational database analyses.

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