Cost-Effectiveness and Budget Impact of Lumacaftor/Ivacaftor in the Treatment of Cystic Fibrosis

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ABSTRACT

BACKGROUND: Cystic fibrosis (CF) is a chronic, progressive, genetic disease affecting more than 30,000 people in the United States and 70,000 people globally. The goals of treatment are to slow disease progression, reduce pulmonary exacerbations, relieve chronic symptoms, and improve the patient's quality of life. Lumacaftor/ivacaftor is a new therapy for CF that has demonstrated good clinical outcomes, including improved absolute percentage predicted forced expiratory volume in 1 second (FEV₁%). However, given the high cost of therapy, there is a need to evaluate the overall value of lumacaftor/ivacaftor in CF management.

OBJECTIVES: To (a) conduct a cost-effectiveness analysis (CEA) of lumacaftor/ivacaftor to understand the overall effectiveness of the drug compared with its costs and (b) conduct a budget impact analysis (BIA) to understand the potential financial effect of introducing a new drug in a health plan.

METHODS: Two static decision models were developed using Microsoft Excel to evaluate the cost-effectiveness and budget impact of lumacaftor/ivacaftor over a 1-year time frame from a payer perspective. Model inputs included drug costs (wholesale acquisition costs), drug monitoring schedules (package inserts), drug monitoring costs (Centers for Medicare & Medicaid physician fee schedule and published literature), FEV₁% predicted and pulmonary exacerbation values (clinical trials), and cost to treat pulmonary exacerbations (published literature). The outcomes in the CEA included total cost of therapy; average cost-effectiveness ratio (ACER), defined as cost per FEV₁% predicted; and incremental cost-effectiveness ratio (ICER), defined as the difference in the ratio of cost per FEV₁% predicted of lumacaftor/ivacaftor and placebo. Outcomes in the BIA included total budget impact; cost per member per month (PMPM), defined as total budget impact per hypothetical plan population; and cost per treated member per month (PTMPM), defined as total budget impact per target CF population. All costs were adjusted to 2016 dollars, and one-way sensitivity analyses were conducted to test the model robustness given uncertainty in model inputs and study assumptions.

RESULTS: The annual cost of therapy per patient for lumacaftor/ivacaftor was \$379,780. The ACER for lumacaftor/ivacaftor was \$151,912, while the ICER for lumacaftor/ivacaftor compared with placebo was \$95,016 per FEV₁% predicted. The annual total budget impact due to the inclusion of lumacaftor/ivacaftor on the health plan formulary was \$266,046. The PMPM cost was \$0.02 and the PTMPM cost was \$620.67.

CONCLUSIONS: In patients with CF, lumacaftor/ivacaftor has demonstrated better clinical effectiveness compared with placebo alongside an increased drug acquisition cost. However, the therapy may be a viable alternative to existing standard therapy over a short time horizon. Health care payers, both private and public, need to evaluate the cost-effectiveness and the financial effect when considering expansion of new drug coverage in CF management.

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What is already known about this subject

- Lumacaftor/ivacaftor was approved by the U.S. Food and Drug Administration in 2015.
- Lumacaftor/ivacaftor has been rejected by international health technology assessments such as the National Institute for Health and Care Excellence of the United Kingdom and the National Centre for Pharmacoeconomics of Ireland because of its poor cost-effectiveness profile and high annual treatment cost per patient.

What this study adds

- Incremental cost-effectiveness ratio (ICER) was used as cost per absolute percentage predicted forced expiratory volume in 1 second (FEV₁%) instead of cost per quality-adjusted life-years (QALY), which is reported in other health technology assessments.
- This study used FEV₁% predicted from the clinical trial because the long-term clinical effectiveness and the transition states possible after treatment initiation were not known.
- In patients with cystic fibrosis and with homozygous F508del mutation, lumacaftor/ivacaftor had an ICER of \$95,016 per FEV₁% predicted compared with placebo.

Cystic fibrosis (CF) is a chronic, progressive, genetic disease that primarily affects the respiratory, digestive, and reproductive organ systems in children and adults.¹ It is primarily characterized by abnormally thick mucus linings in the lungs resulting in reduced function and development of potentially fatal respiratory infections.² The disease is inherited in an autosomal recessive pattern and is caused by various mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene, which affects the composition of the mucous layer lining the epithelial cells in the lungs and pancreas.³ This leads to disruption of ion transport and changes in the amount of water and texture of mucus in cell linings of the lungs.³ In addition to being associated with respiratory dysfunction, CF also affects the digestive system and reproductive system, hastening disease progression and shortening life expectancy.^{4,5}

CF is a relatively uncommon diagnosis, with an estimated prevalence of 30,000 people in the United States and more than 70,000 people globally in 2013.² In the United States, approximately 1,000 new cases of CF are diagnosed each year with more than 75% of individuals diagnosed by 2 years of

age.² Severity of illness is assessed by the absolute percentage predicted forced expiratory volume in 1 second (FEV₁% predicted), with >70% categorized as mild, 40%-69% as moderate, and <40% as severe.⁶

Despite a low prevalence, the costs of illness are significant. In 2011, the annual estimated average costs of CF care were \$30,000, \$57,000, and \$215,000 for patients with mild, moderate, and severe disease, respectively. Costs were reported to be the highest among children aged 10-14 years and lowered with increasing age through 45 years across all 3 disease severity groups. Specifically, severe disease in patients aged 10-14 years incurred a much higher annual cost of care (\$343,900) when compared with mild disease in patients aged 40-44 years (\$15,600).⁷

There is no definitive cure for CF, so the goals of current therapy focus on slowing disease progression, reducing pulmonary exacerbations, relieving chronic symptoms, and improving the patient's quality of life.⁸ Existing treatments for the pulmonary manifestations of CF include broad maintenance therapies that help to clear mucus from the lungs and to prevent or treat pulmonary infections. However, in recent years, new treatments for CF have been introduced. The U.S. Food and Drug Administration (FDA) approved a CFTR modulator therapy called ivacaftor (Kalydeco) in 2012 and later in 2015 as lumacaftor/ivacaftor.^{9,10} Ivacaftor is indicated in patients aged 6 years and older who have the G551D mutation in the CFTR gene, which includes approximately 4% of patients with CF. Lumacaftor/ivacaftor is indicated in patients aged 6 years and older who have the F508del mutation in the CFTR gene, including approximately 45% of patients, and significantly expands treatment utility.

Two major phase 3 clinical trials of lumacaftor/ivacaftor, TRAFFIC and TRANSPORT, demonstrated significant improvements in FEV₁% predicted values from baseline among patients receiving the drug—ranging from 2.6 to 3 units change in FEV₁% predicted across the studies and in the pooled analysis.¹⁰⁻¹² Data from the pooled analysis also demonstrated a 30% to 39% reduction in the rate of pulmonary exacerbations among patients who received lumacaftor/ivacaftor compared with placebo.¹³ Although lumacaftor/ivacaftor has demonstrated higher efficacy, lower side effects, and, most importantly, has offered a new treatment option to patients with CF with the F508del mutation, the estimated wholesale acquisition cost of \$270,172.77 in 2016 has become a source of concern for health care stakeholders.¹⁴ Despite the clinical benefits, the high cost of therapy necessitates an assessment of the overall value of the drug in terms of its cost-effectiveness and the financial impact on health plans.

Since the launch of lumacaftor/ivacaftor, several health technology assessments (HTA) have provided additional data. In 2015, the National Centre for Pharmacoeconomics (NCPE) of Ireland compared lumacaftor/ivacaftor with the standard of

care and estimated an incremental quality-adjusted life-years (QALY) gain of 2.45 at an incremental cost of €903,947 (U.S. \$1,017,103.08 in 2016). The incremental cost-effectiveness ratio (ICER) was estimated at €369,141 per QALY (U.S. \$415,350 in 2016).¹⁵ In 2016, the National Institute for Health and Care Excellence (NICE) of the United Kingdom also issued a draft guidance against recommending lumacaftor/ivacaftor for treating CF, citing a high annual treatment cost of €104,000 (U.S. \$118,560 in 2016) per patient as the reason for its decision. Similarly, the Scottish Medicines Consortium did not recommend adoption of lumacaftor/ivacaftor.¹⁶ Despite these assessments, little information is available relevant to decision making in the United States, and there is a dearth of evidence from published literature regarding the drug's cost-effectiveness and affordability. Thus, it is important to assess the cost-effectiveness and budget impact for lumacaftor/ivacaftor from a U.S. health care payer perspective.

This study's objectives were to (a) conduct a cost-effectiveness analysis (CEA) of lumacaftor/ivacaftor to understand the overall effectiveness of the drug compared with its costs and (b) conduct a budget impact analysis (BIA) to understand the potential financial effect of introducing a new drug in a health plan.

Methods

Model Characteristics

Two static decision models were developed using Microsoft Excel 2013 (Microsoft, Redmond, WA) to evaluate the cost-effectiveness and budget impact of lumacaftor/ivacaftor in a hypothetical CF population. Both models were analyzed over a 1-year time frame. A shorter time frame was chosen to be consistent with the length of phase 3 clinical trials and the outcomes data from the trials.¹⁷ In addition, there was a lack of data on long-term clinical efficacy of the drug at the time of the study. Data up to 96 weeks from the phase 3 PROGRESS trial are available, which followed treatment and placebo groups from phase 3 TRAFFIC and TRANSPORT trials. While the treatment group in the trial continued on lumacaftor/ivacaftor from week 24 to week 96, the placebo group rolled over from no treatment to different doses of lumacaftor/ivacaftor after 24 weeks. Also, the primary outcome of this trial was long-term safety of the combined therapy, and the treatment groups were compared with a cohort of matched control patients who were also homozygous for the F508del-CFTR mutation from the Cystic Fibrosis Foundation Patient Registry.¹⁸ These reasons necessitated using a shorter time horizon and static decision models.

This study was analyzed from a U.S. third-party payer perspective and direct costs such as drug acquisition costs, monitoring costs, and costs to treat adverse events were included in the analyses.

The hypothetical patient population in both analyses was CF patients aged 12 years and older with homozygous F508del mutation of the CFTR gene who were on standard therapy at baseline and treated by lumacaftor/ivacaftor. The demographics

TABLE 1 Safety and Efficacy of Lumacaftor/Ivacaftor from Phase 3 and Published Clinical Trials^{11,12}

	TRAFFIC ¹¹		TRANSPORT ¹²		Pooled Analysis	
	Placebo (n = 184)	Lumacaftor/ Ivacaftor (n = 182)	Placebo (n = 187)	Lumacaftor/ Ivacaftor (n = 187)	Placebo (n = 371)	Lumacaftor/ Ivacaftor (n = 369)
Efficacy at week 24						
Absolute change in FEV ₁ from baseline, mean (SE)	-0.44 (0.52)	2.16 (0.53)	-0.15 (0.54)	2.85 (0.54)	-0.29 (0.53)	2.50 (0.53)
Percentage difference vs. placebo in absolute change, mean (95% CI)	–	2.6 (1.2-4.0)	–	3.0 (1.6-4.4)	–	2.8 (1.8-3.8)
Safety at week 48						
Participants affected or at risk for pulmonary exacerbations, n (%)	112 (60.86) ¹⁰	73 (40.10) ¹⁰	139 (74.33) ¹⁰	79 (42.24) ¹⁰	182 (49.2) ^{17,a}	132 (35.8) ^{17,a}
Participants discontinued because of an adverse event, n (%)	–	–	–	–	6 (1.6) ^{17,a}	17 (4.6) ^{17,a}

^aThe reported adverse events were those that either developed or increased in severity at or after the time patients received the initial dose of the study drug (placebo or lumacaftor/ivacaftor) up to 28 days after receipt of the last dose.

CI=confidence interval; FEV₁=percentage predicted forced expiratory volume in 1 second; SE=standard error.

and clinical characteristics of the study population were based on clinical trial data of lumacaftor/ivacaftor.¹⁷

Lumacaftor/ivacaftor does not replace any existing therapy, since the drug targets a specific gene mutation. Thus, the CEA compared lumacaftor/ivacaftor with placebo, although both groups were on standard therapy consisting of maintenance therapies at baseline. The budget impact was calculated based on preinclusion and postinclusion of the drug in the formulary consisting of standard therapy, including pulmonary medications such as bronchodilators, inhaled antibiotics, dornase alfa, inhaled hypertonic saline, and inhaled corticosteroids.¹⁷

The outcomes of interest for the CEA included cost of therapy per patient; average cost-effectiveness ratio (ACER), presented as cost per FEV₁% predicted per patient; and ICER, presented as additional cost per 1-unit increase in FEV₁% predicted per patient. The average ratio is particularly useful if the new treatment does not have any comparators, and the adoption of a new treatment is based on its cost-effectiveness profile compared with a placebo/standard therapy. The incremental ratio summarizes the cost-effectiveness of a new treatment over its comparators by considering cost and outcomes. When multiple comparators are available, ACER may not be fully useful and instead ICER is considered.¹⁹ Given that the comparators are limited for lumacaftor/ivacaftor, both ACER and ICER were calculated using the placebo group as the comparator. The total cost of therapy was calculated as the sum of all costs, including drug costs, monitoring costs, and costs to treat adverse events involved in placebo or lumacaftor/ivacaftor treatment.

The ACER was calculated as total cost of therapy per FEV₁% predicted at week 24 derived from a pooled analysis of the phase 3 clinical trials. The ICER was calculated as $(\text{Cost}_{\text{lumacaftor/ivacaftor}} - \text{Cost}_{\text{Placebo}}) / (\text{Outcome}_{\text{lumacaftor/ivacaftor}} - \text{Outcome}_{\text{Placebo}})$, where the outcome is FEV₁%

predicted at week 24 from a pooled analysis of the phase 3 clinical trials.

The outcomes of interest for the BIA included total budget impact, per member per month (PMPM) cost, and per treated member per month (PTMPM) cost. The total budget impact was calculated as the difference in budget preinclusion and postinclusion of lumacaftor/ivacaftor to the health plan formulary. The PMPM cost was calculated as total budget impact divided by total hypothetical plan population (1 million) divided by 12. The PTMPM cost was calculated as total budget impact divided by total target population (35.72) divided by 12.

Efficacy Inputs

The FEV₁% predicted value was used as the efficacy input in the CEA model as it was the most commonly reported primary outcome in the phase 3 clinical trials of lumacaftor/ivacaftor (Table 1). Mean absolute change in FEV₁% predicted, reported at Week 24 in the clinical trials, was used in the analyses. The safety data on the drug included the most common adverse events reported by subjects in the phase 3 clinical trials. The most common adverse events were defined as those that occurred in at least 10% of patients in any treatment group.¹⁷

Cost Inputs

Drug Acquisition Costs. The drug acquisition costs, reported as the wholesale acquisition cost, were taken from the 2015 RED BOOK dosage information from FDA package inserts. Number of doses per package from RED BOOK were used to calculate the number of packages required per patient per year. For both analyses, the drug acquisition cost was calculated as the product of the package cost and the number of packages required per year. Product rebates, discounts, patients' copay or coinsurance were not considered in the analyses. The dose,

TABLE 2 Dosing and Acquisition Costs of Lumacaftor/Ivacaftor and Standard Therapy^{10,17}

Drug	Dose, Frequency, Route	Doses per Pack	Wholesale Acquisition Price per Package (\$)	Packages Needed per Year	Wholesale Acquisition Price per Year 2016 (\$)
Lumacaftor/ivacaftor (Orkambi) ^a	400 mg lumacaftor + 250 mg ivacaftor Q12 hours PO12 hours	112.0	19,923.08	13.03	270,172.77
Bronchodilator Albuterol (Proventil HFA) ^{39,b}	0.18 mg Q6 hours inhalation	74,444.0	75.36	0.04	2.93
Inhaled antibiotic Tobramycin (Tobi) ⁴⁰	300 mg Q12 hours inhalation	56.0	3,604.00	13.00	46,852.00
Mucolytic agent Dornase alfa (Pulmozyme) ⁴¹	2.5 mg Q daily inhalation	30.0	3,283.41	12.16	39,926.26
Mucolytic agent Hypertonic saline (NebuSal) ⁴²	10 ml of 6% solution Q12 hours inhalation	24.0	40.00	30.40	1,216.00
Inhaled corticosteroid Fluticasone (Flonase) ^{43,c}	200 mcg Q daily inhalation	9.9	11.84	147.40	1,745.21

^aEach tablet contains 250 mg lumacaftor/125 mg ivacaftor.

^bTwo doses every 6 hours.

^cTwo 50 mcg sprays in each nostril once daily.

PO=by mouth; Q=each or every.

frequency, route of administration, and acquisition cost of lumacaftor/ivacaftor and standard therapy are presented in Table 2.

Monitoring Costs. The monitoring schedules used in both analyses were taken from the package insert of lumacaftor/ivacaftor and CF care guidelines reported by the 2013 CF Foundation Patient Registry data.^{10,20} There were no administration costs included in the analyses, since the drugs were administered either by mouth or inhalation. Monitoring test schedules associated with lumacaftor/ivacaftor included aspartate aminotransferase test (AST), alanine aminotransferase test (ALT), and bilirubin, which were taken from the package insert. All other laboratory tests were taken from guidelines published by the CF Foundation. Frequency of clinic visits, outpatient visits, and inpatient stays were taken from published literature.^{10,20} The costs for laboratory and monitoring tests were obtained from the Centers for Medicare & Medicaid (CMS) 2016 Physician Fee Schedule using the Current Procedural Terminology codes, 2016 Healthcare Bluebook, and from published literature.^{21,22} The drug monitoring test schedules and annual costs are presented in Table 3.

Cost to Treat Adverse Events. Common adverse events were defined as those that occurred in at least 10% of patients in any treatment group. Pulmonary exacerbation was the most commonly reported serious adverse event in the phase 3 clinical trials of lumacaftor/ivacaftor, and the cost to treat the adverse event was taken from published literature (Table 3).^{17,23} The probabilities of medical events and adverse events were calculated based

on the event rate in each group (Appendix A, available in online article). All costs were adjusted to 2016 U.S. dollars using the medical care (drug costs) and medical care services (monitoring costs) components of the Consumer Price Index.²⁴

Model Assumptions

Several assumptions were made in the study and are summarized as follows:

1. A recently published study reported that the mean weighted medication possession ratio of the CF population for lumacaftor/ivacaftor was 92.28% with a range of 87%-99.5%.²⁵ To provide a fair comparison and avoid preference for lumacaftor/ivacaftor therapy, adherence to lumacaftor/ivacaftor, placebo (CEA), and standard therapy (BIA) were assumed to be 100%.
2. The prevalence of CF was based on the latest estimates available from 2015 CF Foundation data, which were assumed to be stable in 2016.
3. Patients were assumed to be maintained on the assigned therapy throughout the duration of the model.
4. The clinical inputs such as FEV₁% predicted values and pulmonary exacerbation rates taken from published phase 3 clinical trials were assumed to be reliable and valid.
5. Because the analyses had a short analytic time frame, it was assumed that both treatment groups did not undergo a transition to lung transplantation or death. This was based on the adverse events reported in the phase 3 clinical trials, which included pulmonary exacerbations and other minor

TABLE 3 Cost of Drug Monitoring and Adverse Events

	Probability	CPT Code	Frequency	Unit Cost 2016 (\$)	Annual Cost 2016 (\$)
Drug monitoring					
AST	1.00	84450 ⁴⁴	4	14.00 ⁴⁵	56.00
ALT	1.00	84460 ⁴⁶	4	14.00 ⁴⁷	56.00
Bilirubin	1.00	82247 ⁴⁸	4	13.00 ⁴⁹	52.00
Sputum/throat cultures	1.00	87070, 87205 ⁵⁰	4	158.40 ⁵¹	633.60
PFT	1.00	94010 ⁵²	2	36.52 ⁵³	73.04
Flu shot	1.00	90656 ⁵⁴	1	24.00 ⁵⁵	24.00
Fat-soluble vitamin blood levels	1.00	A: 84590 ⁵⁶ D: 82306 ⁵⁷ E: 84446 ⁵⁸ K: 84597 ⁵⁹	2	A: 31.00 ⁶⁰ D: 100.00 ⁶¹ E: 37.00 ⁶² K: 36.00 ⁶³	408.00
OGT	1.00	82951, 82952 ⁶⁴	1	34.00 ⁶⁵	34.00
Clinic visits	0.56 ^a	99205 (initial) 99215 (subsequent) ⁶⁶	4.39 ⁶⁷	562.50 ^b	1,382.85
Outpatient visits	0.55 ^a		6.26 ⁶⁷	291.18 ^b	1,002.53
Inpatient stays	0.28 ^a		0.64 ⁶⁷	7,377.05 ^b	1,321.96
Adverse events					
Pulmonary exacerbations in placebo group	0.39 ^c		3.6 ⁶⁸	13,612.65 ²³	19,112.14
Pulmonary exacerbations in lumacaftor/ivacaftor group	0.31 ^c		3.6 ⁶⁸	13,612.65 ²³	15,191.71

^aCalculated using rate of medical events from O'Sullivan et al. (2011).⁶⁷

^bCalculated using Medical Expenditure Panel Survey 2014 data.⁶⁹

^cCalculated using rate of pulmonary exacerbations in placebo group and lumacaftor/ivacaftor group reported in phase 3 clinical trial.¹²

AST=aspartate aminotransferase test; ALT=alanine aminotransferase test; CPT=Current Procedural Terminology; PFT=pulmonary lung function test; OGT=oral glucose tolerance test.

events such as cough, increased sputum, headache, hemoptysis, and nasopharyngitis.¹⁷ This assumption may not be relevant to studies with a longer time horizon.

- In the CEA, subjects were assumed to be on standard therapy at baseline, which included maintenance drugs.
- Because lumacaftor/ivacaftor is a novel CFTR modulator therapy, budget impact was calculated to understand the financial effect on a health plan based on preinclusion and postinclusion of the drug on the formulary. The assumption was that the patients continued to receive existing standard therapy consisting of pulmonary medications such as bronchodilators, inhaled antibiotics, dornase alfa, inhaled hypertonic saline, and inhaled corticosteroids before and after the introduction of lumacaftor/ivacaftor.
- For both analyses, cost due to medical events including clinic visits, outpatient visits, and inpatient stays were assumed to decline by 10% after the initiation of lumacaftor/ivacaftor therapy because there were no negative outcomes observed in clinical trials after the initiation of lumacaftor/ivacaftor. Although counterintuitive given the positive outcomes, 2 directional sensitivity analyses were conducted for these medical events to test the worst-case and best-case scenarios. The cost of pulmonary exacerbations was adjusted based on the probabilities obtained from published clinical trials.

Sensitivity Analysis

To account for uncertainty in study variables, univariate or one-way sensitivity analyses were conducted to determine the impact of varying the model inputs in the CEA and BIA of lumacaftor/ivacaftor. Drug acquisition costs, drug monitoring costs, cost to treat pulmonary exacerbations, and inflation rates were varied over a range of estimates ($\pm 25\%$) to test the robustness of the results based on the ranges used in the literature.²⁶⁻²⁸

Results

Base-Case Analysis: Cost-Effectiveness of Lumacaftor/Ivacaftor

The total cost of therapy per patient—defined as the sum of all the costs including drug costs, monitoring costs, and costs to treat adverse events in the lumacaftor/ivacaftor group—was \$379,780 compared with \$113,735 in the placebo group. The ACER for lumacaftor/ivacaftor was \$151,912, indicating a positive change in FEV₁% predicted value from baseline. The ACER for placebo was -\$392,188. The estimated ICER of lumacaftor/ivacaftor over placebo was \$95,016, indicating the additional cost of a 1-unit positive change in FEV₁% predicted value by lumacaftor/ivacaftor compared with the placebo group.

Sensitivity Analysis: Cost-Effectiveness of Lumacaftor/Ivacaftor

After a $\pm 25\%$ change in the cost of lumacaftor/ivacaftor, the drug had an ICER ranging from \$70,894 to \$119,139. Similarly, lumacaftor/ivacaftor was sensitive to changes in inflation rate

FIGURE 1 Tornado Plot for One-Way Sensitivity Analysis of Cost-Effectiveness of Lumacaftor/Ivacaftor

AST = aspartate aminotransferase test; ALT = alanine aminotransferase test; ICER = incremental cost-effectiveness ratio; PFT = pulmonary lung function test; OGT = oral glucose tolerance test.

with the ICER ranging from \$70,843 to \$119,054, cost of standard therapy with the ICER ranging from \$87,004 to \$103,029, cost to treat pulmonary exacerbations with the ICER ranging from \$93,660 to \$96,373, and probability of occurrence of pulmonary exacerbations with the ICER ranging from \$93,791 to \$96,241. The ICER of lumacaftor/ivacaftor was not affected by varying the cost of other variables and probabilities of occurrence of medical events. Figure 1 presents a tornado plot for the one-way sensitivity analysis of cost-effectiveness of lumacaftor/ivacaftor. Input ranges were plotted to determine the effect of different variables on the ICER.

Base-Case Analysis: Budget Impact of Lumacaftor/Ivacaftor

The prevalence of CF in the entire U.S. population was estimated at 0.00897%, with an extrapolated estimate of CF prevalence in those aged 12 years or above calculated as 24,609 of 274,062,018 (0.00897%; Appendix B, available in online article).^{29,30} Similarly, the prevalence of CF in a hypothetical plan population of 1 million was estimated at 89.70. Of the

89.70, 77.50 (86.4%) were estimated to have the F508del mutation, with 46.1% of those qualifying with homozygous F508del mutation, leading to the target population estimation of 35.72.²⁰ Using these estimates, the cost of therapy per patient for standard therapy alone before the inclusion of lumacaftor/ivacaftor was \$113,735 and after the inclusion of lumacaftor/ivacaftor on the formulary was \$379,780. Hence, the total budget impact due to inclusion of the drug on the formulary was \$266,046. Based on a hypothetical plan population of 1 million individuals, the PMPM cost was \$0.02, with the PTMPM cost of \$620.67 based on 35.72 treated population.

Sensitivity Analysis: Budget Impact of Lumacaftor/Ivacaftor

After a $\pm 25\%$ change in the cost of lumacaftor/ivacaftor, the drug had the PTMPM cost ranging from \$410.75 to \$830.59. Similarly, lumacaftor/ivacaftor was sensitive to change in inflation rate with the PTMPM ranging from \$462.76 to \$777.69, change in cost to treat pulmonary exacerbations with the PTMPM cost ranging from \$611.81 to \$629.53, and probability

FIGURE 2 Tornado Plot for One-Way Sensitivity Analysis of Budget Impact of Lumacaftor/Ivacaftor

ALT=alanine aminotransferase test; AST=aspartate aminotransferase test; PFT=pulmonary lung function test; OGT=oral glucose tolerance test; PTMPM=per treated member per month.

of occurrence of pulmonary exacerbations with the PTMPM cost ranging from \$611.52 to \$628.67. The PTMPM cost of lumacaftor/ivacaftor was not affected by varying the cost of other variables and probabilities of occurrence of medical events. Figure 2 presents the tornado plot for the one-way sensitivity analysis of the budget impact of lumacaftor/ivacaftor. Input ranges were plotted to determine the effect of different variables on the PTMPM cost.

Discussion

CFTR modulator therapies have revolutionized the treatment paradigm for CF patients. With changing health care policies and reimbursement patterns, managing health care costs is critical. Insurance companies are increasingly demanding health economic evidence to support their formulary decisions. The CFTR modulator therapies have good clinical effectiveness, including an increase in FEV₁% predicted values, improvement in revised CF questionnaire (CFQR) scores, improved body mass index, and reduction in pulmonary exacerbation events. These regimens, therefore, have the potential

to increase median life expectancy and delay the occurrence of death. But, the annual cost of lumacaftor/ivacaftor is estimated to be \$270,000, and its overall affordability is not established. Given the unmet need, this study was conducted to understand its value for the cost in the U.S. health care system. As there are no published studies that have assessed the cost-effectiveness of lumacaftor/ivacaftor in a U.S. population, the results of this study can be discussed within the context of published international studies. The HTA conducted by the NCPE of Ireland evaluated lumacaftor/ivacaftor compared with the standard of care using a lifetime simulation model and estimated an ICER of €369,141 per QALY (U.S. \$415,350 in 2016).¹⁵ The major differences between this study and NCPE HTA were the source of data and choice of clinical endpoints. The model inputs for NCPE HTA were provided by a single nonpublic source, whereas this study was conducted as a part of academic research and model inputs were taken from public sources like the CMS Physician Fee Schedule, RED BOOK, and published literature. The NCPE HTA used QALY as a clinical outcome, whereas this study used FEV₁% predicted as the clinical

endpoint. QALY is preferred in a cost-utility analysis or a CEA when utilities for each transition state and long-term clinical effectiveness is known. But this study used FEV₁% predicted because the long-term clinical effectiveness and the transition states possible after treatment initiation were not known at the time this study was conducted.

While cost-effectiveness thresholds in the form of cost per QALY are commonly used in the United Kingdom, Canada, and Australia to make new treatment approval decisions, there are isolated cases of its use in the United States.³¹ Different value frameworks in the United States, list different thresholds, but generally, treatments under \$50,000 per QALY gained are considered of “high value.” Recently, the World Health Organization used the country’s gross domestic product to set thresholds, which, for the United States, would have translated as “intermediate value” or “somewhat cost-effective” for thresholds within the range of \$100,000 to \$150,000 and “economically unattractive” or “low value” over \$150,000 per QALY.³² Given that the ICER of lumacaftor/ivacaftor in this study was \$95,016 per FEV₁% predicted, there is a need for payers to further examine the treatment in light of the value frameworks, including their budget needs and patient needs.

The CFTR modulator therapies are the only available disease-modifying therapies that have the potential to increase median life expectancy in CF patients. A similar scenario was observed for nintedanib and pirfenidone, first-in-class medications approved recently for the treatment of idiopathic pulmonary fibrosis. A CEA conducted from a U.K. payer perspective concluded that the lifetime ICER was £145,310 per QALY gained (U.S. \$183,762.35 per QALY in 2016) for nintedanib and £172,198 per QALY gained (U.S. \$217,564.54 per QALY in 2016) for pirfenidone compared with placebo.³³ These disease-modifying therapies have shown significant differences versus placebo in improving acute exacerbation events and lung function decline. Hence, the possible increase in life expectancy with newer treatments may be a justification for accepting the higher ICERs in the United States. The results of the sensitivity analysis suggest that after varying the data input ranges, lumacaftor/ivacaftor therapy was stable to drug monitoring schedules but were sensitive to variability in cost of the drug, inflation rates, cost of standard therapy, and cost and probability of pulmonary exacerbations. However, the ICER of lumacaftor/ivacaftor was most likely to be influenced by change in the cost of the drug, standard therapy, and cost to treat pulmonary exacerbations.

A BIA is an essential part of a comprehensive economic assessment of a new treatment and is increasingly being requested by payers, along with a CEA, before formulary approval or reimbursement. The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health care intervention within a specific health care setting to

understand any resource constraints. There were no previous studies in the United States that assessed the affordability of lumacaftor/ivacaftor. However, the BIA conducted by NCPE on a target population of 505 patients assessed an annual cost for lumacaftor/ ivacaftor at €158,306 (U.S. \$178,122 in 2016) and a 1-year budget impact of €78,378,536 (U.S. \$92,736,703 in 2016) and concluded that the budget impact due to lumacaftor/ ivacaftor was significant with an associated opportunity cost.¹⁵

In comparison, this study’s 1-year budget impact of lumacaftor/ivacaftor per member was \$264,000 (\$0.022×1 million×12 months) and per treated member was \$266,044 (\$620.67×35.72×12), similar to the findings of NCPE, indicating a significant economic impact on the U.S. health care budget. Although the Institute for Clinical and Economic Review has published an annual threshold of \$904 million for estimated potential budget impact for each individual new molecular entity for 2016 within the United States,³⁴ decisions regarding BIAs are made purely by the payers, and most of these decisions are contingent on the balance between the increase in PMPM and PTMPM costs and the need of individual patients. The results of the sensitivity analysis suggest that even after varying the data input ranges, lumacaftor/ivacaftor therapy was stable to most of the variables except for the cost of the drug, inflation rates, and pulmonary exacerbation.

Lumacaftor/ivacaftor is listed as a specialty tier, requires prior authorization, or is not listed under some formularies, indicating reduced access to the CF population.³⁵⁻³⁷ Lumacaftor/ivacaftor is covered under Medicare Part D with a typical copay range from \$6,014 to \$24,057. Because CF is more prevalent in children and young adults, Medicare might not cover the largest proportion of CF patients. However, with an average monthly copay of \$1,252 for those who are covered under Medicare, patients reach the donut hole (coverage gap of \$3,310 in 2016) in the third month, which makes the patients responsible for a major part of their prescription costs. Once patients go beyond the donut hole (also called catastrophic coverage, \$4,850 in 2016), Medicare once again covers most of the drug costs.³⁸

The findings of this analysis can be used by payers and policymakers to predict how a change in the use of lumacaftor/ ivacaftor can affect the trajectory of CF-related spending. These results can be used for budget planning, forecasting, and calculating the effect of health technology changes on premiums in health insurance schemes. This study has major implications for payers and providers in their selection of cost-effective and affordable treatments for patients with CF.

Limitations

Although our study is one of the few studies to conduct a pharmacoeconomic evaluation of lumacaftor/ivacaftor, there are some limitations to consider. First, there were no existing comparator

drugs, since lumacaftor/ivacaftor is indicated for CF patients with homozygous F508del mutations, hence, the evaluations involved comparisons against placebo or standard therapy.

Second, standard therapy available in the market consisted of maintenance therapies; our study was restricted to the standard therapy mentioned in the published clinical trials of lumacaftor/ivacaftor, which did not include drugs used to treat complications due to CF.

Third, cost inputs and probabilities of events used in the models were obtained from multiple sources, including Medicare reimbursements, Healthcare Bluebook, and published literature. Although one-way sensitivity analyses were conducted to vary input ranges, the resulting estimates of any modeling study need to be treated with some degree of caution.

Fourth, it was not possible to develop dynamic models consisting of transition state probabilities, since lumacaftor/ivacaftor was not approved until 2015. Long-term clinical effectiveness and events after the use of the drug were not available at the time of this study.

Fifth, the clinical efficacy of both treatment groups identified from the TRAFFIC and TRANSPORT trials may not be a true representation of the U.S. CF population, since the trials were multinational and the study population was identified from about 90 sites. This study conducted only univariate sensitivity analyses to test for uncertainty in the model parameters. Finally, the analyses assumed 100% adherence to treatment and stable prevalence of CF across 2015-2016, which may differ from real-world scenarios.

Conclusions

In patients with CF, lumacaftor/ivacaftor has demonstrated better clinical effectiveness compared with placebo alongside significant costs of therapy. However, novel CFTR modulator therapies offer new disease-modifying benefits to patients with CF and may be considered an appropriate alternative to the existing standard therapy. Although the analysis focused on clinical outcomes and cost, decision makers selecting lumacaftor/ivacaftor may be influenced by multiple factors including adverse event profile, ease of administration, clinical outcomes, and coverage policies. The results may not be generalizable beyond a 1-year time horizon, especially if serious adverse events associated with lumacaftor/ivacaftor play a role in influencing the overall cost. The results of this study will assist payers in making better decisions regarding the choice of lumacaftor/ivacaftor over a 1-year period for patients with cystic fibrosis and with homozygous F508del mutation.

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APPENDIX A Probabilities of Medical Events⁶⁷

Variable	Number Considered for Analysis	Discontinued	Number with the Event, n (%)	Group Followed Until (years)	Patient Years	Rate of Event	Probability
Clinic visits	1,064	0	862.0 (81.01)	1	1,064	0.810	$1 - 0.444 = 0.555$
Outpatient visits	1,064	0	860.0 (80.80)	1	1,064	0.808	$1 - 0.445 = 0.554$
Inpatient stays	1,064	0	359.0 (33.76)	1	1,064	0.337	$1 - 0.713 = 0.286$
Placebo ^a	371	6	185.0 (49.80)	0.9	334	$185/334 = 0.55$ $(182 + 6/2)^b$	$1 - 0.609 = 0.391$
Lumacaftor/ivacaftor ^a	369	17	140.5 (38.00)	0.9	332	$140.5/332 = 0.42$ $(132 + 17/2)^b$	$1 - 0.685 = 0.314$

^aHalf considered to be followed until 24 weeks.¹⁷

^bTotal number with the event was calculated as the sum of those with the event and half of those who discontinued; patient years = number considered for analysis multiplied by the time followed; rate of event = number with event/patient years; probability = $1 - e^{-r \cdot t}$ where r = rate of medical event and t = time horizon (1 year).

APPENDIX B Target Population for Budget Impact Analysis of Lumacaftor/Ivacaftor

CF = cystic fibrosis.