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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

LUMACAFTOR/IVACAFTOR (ORKAMBI)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: For the treatment of cystic fibrosis in patients 6 years of age and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.

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Abbreviations

CDR	CADTH Common Drug Review
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
ICER	incremental cost-effectiveness ratio
LUM/IVA	lumacaftor/ivacftor
ppFEV$_1$	per cent predicted force expiratory volume in one second
QALY	quality-adjusted life-year
SoC	standard of care

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	lumacaftor/ivacaftor (Orkambi)
Study Question	What is the cost-effectiveness of lumacaftor/ivacaftor (LUM/IVA) + standard of care (SoC) versus SoC alone for the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del-CFTR mutation
Type of Economic Evaluation	Cost-utility analysis
Target Population	Cystic fibrosis patients age six years and older who are homozygous for the F508del-CFTR mutation
Treatment	LUM/IVA + SoC
Outcome	Quality-adjusted life-years (QALYs)
Comparator	SoC comprising nutritional support, airway clearance, and treatment of clinical manifestations such as lung infections
Perspective	Canadian public health care payer
Time Horizon	Lifetime (119 years)
Results for Base Case	The incremental cost per QALY gained (ICER) for LUM/IVA in patients aged six and over is $446,529.
Key Limitations	• The model does not allow assessment for the validity of the simulation techniques employed given the lack of transparency. This made it challenging to fully assess the coding of the model. • The cumbersome nature of the model does not facilitate conduct of probabilistic analysis, the run time was excessively long. • The new clinical data are provided for patients in the six year to 11 year age group with open-label extension study information available for those aged 12+; however, no new data with respect to the relative efficacy of LUM/IVA compared with SoC was provided. Given this, stratified analysis should have been conducted to better understand the cost-effectiveness of LUM/IVA in the new subpopulation and to see whether the results differ based on the new modelling approach. • Inappropriate assumptions were considered with respect to: o continued benefit with respect to $ppFEV_1$ o benefit in terms of exacerbation rates o treatment costs — the manufacturer assumed an 82% reduction in treatment costs after 12 years (due to loss of market exclusivity), which was not appropriate.
CDR Estimates	• The CDR approach to addressing each of the three issues (treatment costs, exacerbation effects, and $ppFEV_1$ effects) has a modest individual effect on the estimated ICER with the assumptions relating to $ppFEV_1$ and treatment costs having greater effect. • It is the synergistic effect of addressing all at the same time that leads to the degree of increase in the ICER within the base case. CDR reanalyses for LUM/IVA compared with SoC: • patients aged 12 and older: ICER is $3.8 million per QALY • patients aged 6 years to 11 years: ICER is $7.3 million per QALY • a 97% price reduction for LUM/IVA is required for an ICER of $100,000 per QALY in either patient group.

CDR = CADTH Common Drug Review; CFTR = cystic fibrosis transmembrane conductance regulator; ICER = incremental cost-effectiveness ratio; LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SoC = standard of care.

Drug	lumacaftor/ivacaftor (Orkambi)
Indication	For the treatment of cystic fibrosis in patients aged six years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene
Reimbursement Request	As per indication
Dosage Form	lumacaftor 200 mg/ivacaftor 125 mg tablets
NOC Date	April 18, 2017
Manufacturer	Vertex Pharmaceuticals (Canada) Incorporated

Executive Summary

Background

Orkambi is a fixed-dose combination tablet containing 200 mg lumacaftor and 125 mg ivacaftor (LUM/IVA). It is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.[1] This is most common CF-causing mutation worldwide and approximately half of all Canadian patients with CF are homozygous for the F508del mutation. LUM/IVA is the first treatment specifically indicated for the treatment of patients who are homozygous for the F508del mutation in the CFTR gene. The manufacturer has requested that LUM/IVA be listed in accordance with the Health Canada–approved indication.[2]

The recommended dose is lumacaftor 400 mg/ivacaftor 250 mg every 12 hours.[1] This represents the lower of the dosages considered in both the TRANSPORT AND TRAFFIC trials.[3,4] At the current marketed price of $170.54 per tablet, the daily cost of treatment per patient with LUM/IVA is $682, or $248,982 annually.[2]

CADTH reviewed LUM/IVA in 2015 for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. CDEC recommended that LUM/IVA not be reimbursed, based on the clinical findings.[5] The price submitted for LUM/IVA in the original submission is the same as the current submission.

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of LUM/IVA + standard of care (SoC) compared with SoC alone in patients with CF who are 6 years of age or older and homozygous for the F508del-CFTR mutation.[6] SoC comprised nutritional support, airway clearance, and treatment of clinical manifestations such as lung infections. The analysis is based on an individual patient simulation model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a lifetime horizon (119 years), from the perspective of the Canadian public health care payer. Clinical efficacy estimates (based primarily on per cent predicted forced expiratory volume in one second [ppFEV$_1$]) were obtained from 809-109, TRAFFIC, TRASPORT clinical trials, and the PROGRESS extension study.[3,4,7-9] In the manufacturer's submission the base results were

based on a population of 6,000 patient profiles randomly drawn from the LUM/IVA clinical trial portfolio, with probabilistic analysis based on 1,000 replications. During each cycle the model updates a patient's age and $ppFEV_1$, leading to an estimate of cycle specific mortality. The manufacturer reported that LUM/IVA + SoC was associated with greater QALYs and higher costs than SoC alone, with an estimated incremental cost per QALY gained of $446,529.

Summary of Identified Limitations and Key Results

The manufacturer's submitted model had a number of major limitations. These included a lack of transparency; limitations and errors within the probabilistic analysis; a failure to stratify by age; and inappropriate assumptions regarding continued benefit with respect to $ppFEV_1$, benefit in terms of exacerbation rates, treatment costs, and withdrawal.

The model lacked transparency, which led to difficulties in assessing the validity of the coding within the model, with particular difficulties in assessing the methods used within the micro-simulation technique adopted. The complexity of the model ultimately led to the necessary probabilistic analysis being too unwieldy to run. To run a simulation with the necessary 5,000 replications could take up to 45 days. Consequently, the CADTH Common Drug Review (CDR) was unable to conduct the required probabilistic analysis and had to rely on results based on a deterministic analysis. Initial analyses were conducted to assess if this approach would give similar results to the probabilistic analysis.

The probabilistic analysis did not meet requisite standards. There were inappropriate assumptions relating to the specification of certain probability distributions and not all uncertain parameters were made probabilistic. For example, annual in-patient costs were assumed to differ by $ppFEV_1$ but the same random number was used to draw the random value for all values for patients on LUM/IVA + SoC. Conversely, in certain instances random draws for cost values were independent when they should have been dependent. For example, the expected values for the annual in-patient costs for a specific $ppFEV_1$ level for LUM/IVA + SoC and SoC alone were assumed the same but a different random number was used to draw the random value for each treatment. Finally, not all uncertain parameters were made probabilistic.

Results were presented for those aged six and over. This is inappropriate for two reasons; first, the CDR submission from 2015 was for those aged 12 and older and no new data with respect to the relative efficacy of LUM/IVA compared with SoC was supplied for this subgroup; and second, CADTH economic guidelines[10] specifically indicate that when input parameters vary by characteristics of patients that are likely to impact results, the analysis should be stratified by these characteristics.

The manufacturer assumed that over time the differences in $ppFEV_1$ between LUM/IVA + SoC and SoC alone would increase. This assumption is not supported by the comparative clinical trial data given that within the clinical trials in both age groups, results suggested that the benefit form $ppFEV_1$ changes occurs in the initial eight weeks of treatment with curves relating to $ppFEV_1$ staying parallel after this period. This suggests a continuance of benefit but not an extension of benefit.

Further, the manufacturer assumed that after 12 years within the model, the cost of LUM/IVA + SoC would be reduced by 82% due to a generic equivalent becoming available. In addition, the manufacturer assumed patient compliance with LUM/IVA would be 96.46%

each year and reduced drug costs accordingly. The basis of these long-term assumptions is highly questionable and is not compliant with CADTH economic guidelines.

Finally, in addition to assuming a relationship to a reduction in exacerbations through improvements in $ppFEV_1$, the manufacturer incorporated an additional assumption of a further 55% reduction in exacerbations with LUM/IVA + SoC after age 12. This is unlikely to be justified and could potentially lead to double counting the potential benefit from LUM/IVA + SoC. In addition, the results of the 809-109 pediatric efficacy trial[7] found a higher rate of exacerbation on LUM/IVA + SoC, yet the manufacturer modelled a reduction in exacerbations rates in this group.

CDR addressed the issues pertaining to treatment costs, exacerbation effects, and $ppFEV_1$ effects in reanalyses. The incremental cost-effectiveness ratio (ICER) for LUM/IVA +SoC versus SoC alone in patients aged 12 and older is $3.8 million per QALY; while the ICER for patients aged six years to 11 years is $7.3 million. A 98.5% price reduction for LUM/IVA is required for the ICER in both populations to be less than $50,000, or 97% for an ICER of $100,000.

Conclusions

The manufacturer estimated that the incremental cost per QALY gained for LUM/IVA for the treatment of CF in patients six years of age and older who are homozygous for the F508del mutation in the CFTR gene was $446,529; as such, a price reduction in excess of 70% is required for LUM/IVA to lead to an ICER of $100,000 per QALY.

CDR found several major limitations with the manufacturer's submission, which suggested that the submitted result was heavily biased in favour of LUM/IVA. CDR reanalysis found that for patients older than 12, the incremental cost per QALY gained for LUM/IVA was $3.8 million. For patients aged between six and 11, the CDR base-case analysis estimated the incremental cost per QALY gained to be $7.3 million. For both patient groups, the CDR base case suggests that a price reduction of 97% is required for an ICER of $100,000.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer's submission involves a cost-utility analysis using a patient-level simulation model comparing lumacaftor/ivacaftor (LUM/IVA) + standard of care (SoC) versus SoC alone.[6] The dose of LUM/IVA considered in the evaluation was lumacaftor 400 mg/ivacaftor 250 mg every 12 hours, while SoC was defined as comprising nutritional support, airway clearance, and treatment of clinical events such as lung infections. The model incorporates a patient population that represents the pooled individual patient data (n = 1,407) from the clinical studies of LUM/IVA.[3,4,7,11] A patient profile was randomly selected from this pool and run through the model in terms of modelling patients' cystic fibrosis (CF) disease progression and associated mortality, costs, and utilities, in addition to clinical events such as exacerbations, adverse events, and lung transplantation. Model cycles were four weeks for the first two years and annual thereafter for a lifetime horizon (119 years).

In the manufacturer's base-case analysis, a sample was drawn from the pooled data with replacement 6,000 times. From this, random values for certain input parameters were drawn and the expected values for costs and clinical effects for LUM/IVA + SoC and SoC alone were estimated. This was repeated 1,000 times and the final expected values for costs and effects were then estimated.

During each cycle, the patient was at risk of various clinical events with associated costs, mortality, and utility values. The patient's risk of death was based on analysis that combined baseline cystic fibrosis-specific mortality with an analysis that identified the impact of patient characteristics on mortality. Thus, mortality in each cycle was primarily a function of age, sex, per cent predicted forced expiry volume in one second ($ppFEV_1$), and weight for age score.

Utility values were derived from the EuroQol 5-Dimensions (EQ-5D) algorithm completed within the TRAFFIC and TRANSPORT studies and were calculated based on a regression analysis that predicted utility value as a function of $ppFEV_1$ and occurrence of exacerbations.[12] Although the methodology for the analysis of utility values appears appropriate, it is only available in an abstract form. Costs were adjusted to 2017, and included LUM/IVA + SoC, annual cost of managing a patient with CF adjusted for $ppFEV_1$, exacerbations, adverse events, and associated lung transplantation. Resource use relating to CF management, lung transplantation, and exacerbations were derived from a combination of an unpublished chart review by Vertex, unpublished data from the CF Canada registry{239} and clinical opinion; which were weighted by costs derived from published literature and provincial fee schedules.[14-18] The annual cost of LUM/IVA was provided by the manufacturer. The manufacturer assumed that the cost of LUM/IVA would decline by 82% after 12 years due to loss of market exclusivity.

Treatment was assumed to impact disease progression through effects relating to $ppFEV_1$, weight for age score, and exacerbation rates. Treatment effects were obtained from the pertinent clinical trials for effects relating to the first 24 weeks of treatment, and from assumptions based on short-term observational studies and clinical opinion for effects

extrapolated for the period 24 weeks until death (up to 119 years). These effects impact utility values, costs, and mortality.

Manufacturer's Base Case

The manufacturer reported, over a lifetime horizon, a quality-adjusted life-year (QALY) gain with LUM/IVA + SoC versus SoC alone of 5.20 with incremental costs of $2.2 million. This leads to an estimated incremental cost per QALY gained of $446,529. The probability that LUM/IVA + SoC was cost-effective was 0% for all values of a QALY up to $300,000.

Table 2: Summary of Results of the Manufacturer's Base Case

	LUM/IVA + SoC	SoC	Incremental (LUM/IVA + SoC vs. SoC)
Total costs	$2,738,444	$414,422	$2,235,590
Life-years	24.48	18.98	5.51
QALYs	22.11	16.90	5.20
Cost per QALY gained			$446,529

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.
Source: Taken in part from the manufacturer's pharmacoeconomic submission.[6]

Summary of Manufacturer's Scenario Analyses

The manufacturer provided a range of scenario analyses, including:

- changes in effect size with respect to $ppFEV_1$ for LUM/IVA + SoC
- different estimates of annual change in $ppFEV_1$ for SoC
- regression analysis for utility values based on the US EQ-5D algorithm
- no reduction in cost of LUM/IVA after 12 years
- different discount rates
- modest deviation in effect sizes relating to exacerbations
- 20% increase and decrease in effect size relating to weight for age z score
- 20% increase and decrease in base exacerbation rates
- changes in utility estimates
- changes in cost parameters.

All analyses resulted in similar findings to the base case with LUM/IVA + SoC more effective but substantially more costly. The ICER varied from $297,584 (discount rate of 0%) to $897,860 (no discount in cost of LUM/IVA after 12 years).

Limitations of Manufacturer's Submission

The model has a number of major limitations. Concerns with the lack of transparency within the model does to some extent limit its applicability to the decision at hand given that the CADTH Common Drug Review (CDR) was unable to verify results obtained through the use of Visual Basic for Applications macros.

- **Lack of transparency:** The design of the model as a patient simulation leads to a lack of transparency that results in difficulties troubleshooting the model design. The model design precludes the ability of CDR to assess the validity of the model as results are

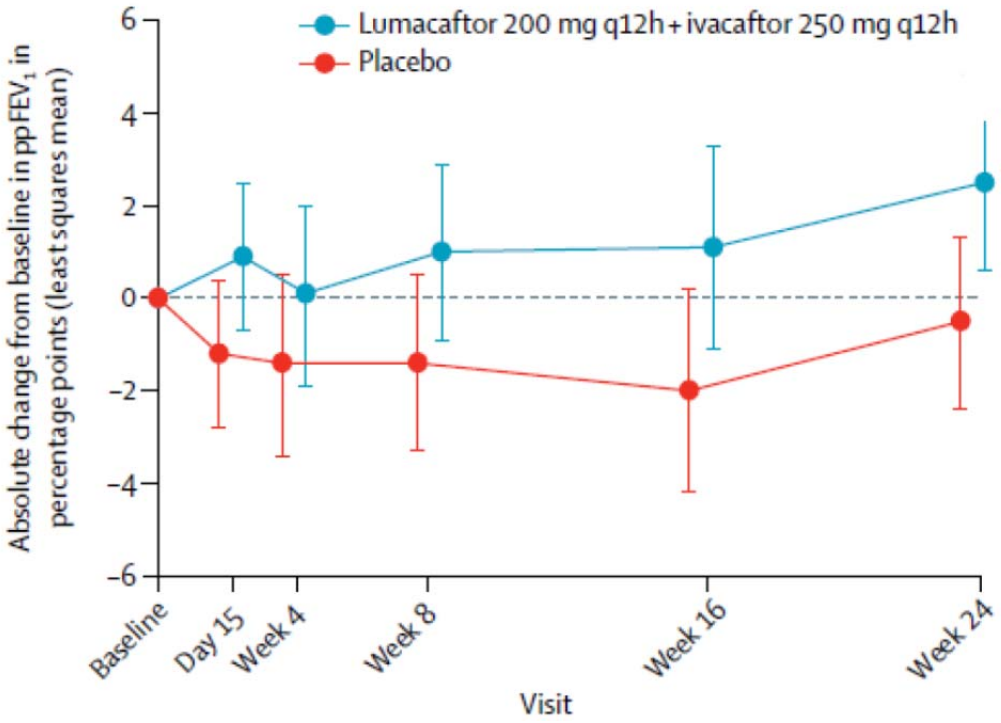
generated by a macro without any ability to verify the chosen values for parameters and whether they reflect the underlying uncertainty and expected values. As such, the model design makes the necessary probabilistic analysis too unwieldy to run — a simulation with only 100 replications took approximately 30 hours to run. Thus, running a simulation with the necessary 5,000 replications could take at least two months. CDR questions the need for such a complex model with a long run time. In light of this, CDR was unable to conduct the required probabilistic analysis and had to rely on results based on a deterministic analysis. Initial analyses were conducted to assess if this approach would give similar results to the probabilistic analysis (see Appendix).

- **Probabilistic analysis:** In addition to concerns with run time, the probabilistic analysis did not meet requisite standards. Some random draws were from curtailed distributions that did not reflect the underlying uncertainty in input values. In certain instances, random draws for cost values were not independent when they should have been independent. For example, annual in-patient costs were assumed to differ by $ppFEV_1$ but the same random number was used to draw the random value for all values for patients on LUM/IVA + SoC. Conversely, in certain instances random draws for cost values were independent when they should have been dependent. For example, the expected values for the annual in-patient costs for a specific $ppFEV_1$ level for LUM/IVA + SoC and SoC alone were assumed the same but a different random number was used to draw the random value for each treatment. Finally, not all uncertain parameters were made probabilistic. For example, the uncertainty around the parameters for the Liou mortality functions[19] is known and provided in the manufacturer's economic report but is not included within the probabilistic analysis.
- **Stratified analysis:** The manufacturer's submission presents analysis for those six years and older. There are two issues pertaining to this presentation of results; first, the previous CDR submission was for those aged 12 and older. No new clinical data with respect to the relative efficacy of LUM/IVA compared with SoC alone was provided for those aged 12 and older in the current submission. Therefore, it is unclear whether there is value in considering this subgroup given the conclusions concerning the cost-effectiveness of LUM/IVA in the previous review and the lack of any data to suggest a change in such conclusions. CADTH Economic Guidelines recommend that when input parameters vary by characteristics of patients that are likely to impact results, the analysis should be stratified by these characteristics.[10] The manufacturer did not provide stratified analyses.

  The major focus of the current review is, therefore, on identifying issues with respect to the analysis pertaining to the six year to11 year age group. CDR reanalysis relating to the population aged 12 years and older is based solely on the issues raised in the previous CDR review. For this population, the CDR reviewer has reanalyzed the existing model adopting the base-case analysis from the previous CDR report. Details of the identified limitations from the previous submission and the necessary reanalysis is provided within Appendix
- **Effects on $ppFEV_1$*:*** The manufacturer makes the assumption that after the initial period represented by the clinical trial, $ppFEV_1$ will decline. This appears reasonable; however, the manufacturer assumes a differential rate of decline favouring LUM/IVA + SoC. This is not based on any long-term evidence. It is important to note that within the 809-109 pediatric efficacy trial, the curves for $ppFEV_1$ appear to be broadly parallel after week 8, which suggests no further incremental treatment effect (Figure 1). None of the manufacture's reported scenario analyses addressed this observation.

CDR adopted a more reasonable assumption, which was to assume the same percentage decline post 24 weeks, as acknowledged by the clinical experts consulted for this review. Note that this is still favourable toward LUM/IVA in that it assumes a continuous treatment effect rather than any potential treatment waning.

Figure 1: Absolute Change in ppFEV$_1$ from Baseline Through Week 24 in 809-109 Study



ppFEV$_1$ = per cent predicted forced expiratory volume in one second.
Source: Manufacturer's pharmacoeconomic submission.[10]

- **Treatment costs:** The manufacturer assumed that compliance with therapy would be 96% and adjusted costs accordingly. No such adjustment was made for treatment effectiveness. Given the likely bias of such an assumption, an alternative assumption assuming 100% compliance was adopted as it was considered more reasonable based on feedback from the clinical experts consulted for this review. Further, the manufacturer assumed that the cost of LUM/IVA would be reduced by 82% after 12 years due to generic equivalents being available. No justification for this assumption is provided and this is counter to CADTH guidance that states that full costs for LUM/IVA for the time horizon of the model should be included.
- **Exacerbation rates:** The manufacturer assumed that LUM/IVA would have an indirect impact on reducing exacerbation rates through reductions in ppFEV$_1$. Furthermore, the manufacturer assumed that LUM/IVA would have a further impact on exacerbation rates after patients reached 12 years of age — an additional 55% reduction in predicted exacerbations. These assumptions are inappropriate as the 809-109 pediatric efficacy trial found a higher rate of exacerbation on LUM/IVA + SoC than with SoC alone. Despite the contrary evidence in the specific population, the CDR reanalysis did assume there was an indirect effect of ppFEV$_1$ on exacerbations, but with no additional relative

reduction. None of the manufacture's reported scenario analyses addressed this concern.

A summary of the three key issues are provided in Table 3.

Table 3: Summary of Key Issues Identified with the Manufacturer's Submission

Issue	Manufacturer's Approach	Identified Limitation	CDR's Revised Approach
Treatment cost	Manufacturer assumes that after 12 years the cost of LUM/IVA will be reduced by 88% due to generic entry.	This assumption is not warranted as there is no guarantee of generic entry, and an 88% reduction may only be achieved if there were three generic entrants.	CDR assumes 100% of drug costs for the duration of treatment.
Exacerbations	For patients aged 12 and older, manufacturer assumes there are two effects: an indirect effect through improvements in $ppFEV_1$ and an additional relative effect from LUM/IVA. For patients aged between six years and 11 years old, manufacturer assumes there is just the indirect effect through improvements in $ppFEV_1$.	For patients aged between six and 11, the clinical trials actually found an increase in exacerbations with LUM/IVA — thus the approach used in this patient group adopts a contrary argument to the approach adopted for those aged 12 and older. If the same approach was adopted, it would be necessary to include a relative increase in exacerbations with LUM/IVA. The approach adopted for those aged 12 and older is likely going to double count the benefits of treatment.	CDR assumed only the indirect effect of $ppFEV_1$ on exacerbations. This may be overestimating the benefit of LUM/IVA on exacerbations in those aged between six and 11.
$ppFEV_1$	The manufacturer assumes that the difference in $ppFEV_1$ between those receiving LUM/IVA and those not will increase each year.	There is no randomized trial data to support this concept. Examination of the effect of treatment on $ppFEV_1$ in the available clinical trials illustrates that the benefit of treatment is obtained within the first eight weeks of treatment and subsequent to that period the difference in $ppFEV_1$. Between the treatment regimens this remains more or less the same.	CDR assumed that the difference in $ppFEV_1$ is maintained for lifetime — this may be a generous assumption as no allowance for treatment waning is considered.

CDR = CADTH Common Drug Review; LUM/IVA = lumacaftor/ivacftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second.

CADTH Common Drug Review Reanalyses

The results of the CADTH base-case analyses are detailed below. Reanalysis that address each of the limitations of the model addressed in the base case are provided separately in Appendix 5. The CDR base cases addresses the three identified limitations as detailed in Table 3.

The analyses demonstrate that for the population aged 12 and older, CDR's approach to addressing each of the three issues (treatment costs, exacerbation effects, and $ppFEV_1$ effects) has a modest individual effect on the estimated incremental cost-effectiveness ratio (ICER), with the assumptions relating to $ppFEV_1$ and treatment costs having greater effect. It is the synergistic effect of addressing all at the same time that leads to the degree of increase in the ICER within the base case. For the population aged between six and 11, the approach to addressing the issue of exacerbation effects has limited impact as the model does not incorporate double counting of impact until age 12. It is the synergistic effect of addressing the $ppFEV_1$ and treatment cost issues at the same time that leads to the degree of increase in the ICER within the base case.

Patients Aged 12 and Older

For patients aged over 12, in the CDR base-case analysis, LUM/IVA + SoC was more costly and more effective than SoC alone. The incremental costs associated with LUM/IVA + SoC were $3.2 million — this was mostly attributed to the incremental drug costs, which were also $3.2 million. The incremental QALY gains with LIM/IVA + SoC were 0.85, leading to an incremental cost per QALY gained of $3.8 million.

Table 4: Summary of CDR Base-Case Results for Patients Aged 12 and Older

	LUM/IVA + SoC	SoC	Incremental (LUM/IVA + SoC vs. SoC)
QALYs	14.79	13.94	0.85
Total costs *Drug costs*	$3,568,869 *$3,213,165*	$364,736 *$0*	$3,204,133 *$3,213,165*
Cost per QALY gained			$3,785,432

CDR = CADTH Common Drug Review; LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Patients Aged Between Six and 11

For patients aged between 6 and 11, in the CDR base-case analysis, LUM/IVA + SoC was more costly and more effective than SoC alone. The incremental costs associated with LUM/IVA + SoC were $5.8 million — this was mostly caused by the incremental drug costs, which were also $5.8 million. The incremental QALY gains with LIM/IVA + SoC were 0.79, leading to an incremental cost per QALY gained of $7.3 million.

Table 5: Summary of CDR Base-Case Results for Patients Aged Between Six and 11

	LUM/IVA + SoC	SoC	Incremental (LUM/IVA + SoC vs. SoC)
QALYs	26.65	25.86	0.79
Total costs *Drug costs*	$6,307,190 *$5,775,150*	$552,207 *$0*	$5,754,983 *$5,775,150*
Cost per QALY gained			$7,258,514

CDR = CADTH Common Drug Review; LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Scenario Analyses

Impact of Extrapolation

Many of the concerns with the manufacturer's submission relate to the methods employed for extrapolation of clinical effect sizes beyond the 24-week time horizon of the clinical trial evidence. Recent CADTH guidance suggests reporting the percentage of estimate incremental benefit obtained by a treatment within the time frame of the available clinical evidence. The manufacturer's submission reported estimated QALY gains of 5.28 over a lifetime horizon. However, when restricting to a time horizon based on the clinical evidence, the estimated QALY gains were 0.001. Thus, only 0.003% of the benefit predicted for LUM/IVA is accumulated during the clinical trial (24 weeks) period, with the rest based on extrapolation rather than direct clinical evidence.

For the CDR reanalysis, the proportion of benefit that was realized during the trial horizon was higher: 0.2% (0.001 out of 0.85 QALYs) for those aged 12 and older, and 0.03% (0.0003 out of 0.79 QALYS) for those aged between six and 11. Thus, within the CDR reanalysis, the vast majority of benefit still occurs within the extrapolation period. This illustrates the degree to which favourable assumptions relating to benefits beyond the trial time horizon can greatly influence results.

Price Reduction Analysis

CDR conducted price reduction analysis to estimate the incremental cost per QALY gained with alternate price reductions for LUM/IVA. Analysis suggested that, based on the manufacturer's submission, a price reduction in excess of 70% was warranted to achieve an ICER of $100,000 per QALY, and a price reduction in excess of 80% was required for an ICER of $50,000. The CDR base case suggests that a price reduction of at least 97% is required to reach an ICER of $100,000, while a reduction in price of 98.5% is warranted for an ICER of $50,000.

Table 6: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs of Submitted Drug Versus Comparator			
Price	**Base-Case Analysis Submitted by Manufacturer (Total Population)[a]**	**Reanalysis by CDR**	
		Aged Between Six and 11	**Aged 12 and Older**
Submitted price	$440,108	$7,258,514	$3,785,432
10% reduction	$394,255	$6,530,119	$3,405,822
20% reduction	$348,401	$5,801,724	$3,026,211
30% reduction	$302,547	$5,073,329	$2,646,601
40% reduction	$256,693	$4,344,934	$2,266,991
50% reduction	$210,839	$3,616,539	$1,887,381

ICURs of Submitted Drug Versus Comparator			
60% reduction	$164,985	$2,888,144	$1,507,770
70% reduction	$119,131	$2,159,749	$1,128,160
80% reduction	$73,277	$1,431,354	$748,550
90% reduction	$27,423	$702,959	$368,940
97% reduction	LUM/IVA + SoC dominates SoC	$110,187	$103,212
98.5% reduction	LUM/IVA + SoC dominates SoC	$49,398	$46,271

CDR = CADTH Common Drug Review; ICUR = incrememental cost-utility ratio; LUM/IVA = lumacaftor/ivacftor; SoC = standard of care.
[a] Based on manufacturer's deterministic analysis.

Issues for Consideration

- The lack of transparency within the model and the required run time made it difficult to validate the analysis provided by the manufacturer, though CDR was able to identify the range of limitations with the submitted model.
- The Institute for Clinical and Economic Review in its Evidence Report found that at the submitted prices LUM/IVA far exceeded standard cost-effectiveness levels.{164} Using thresholds for cost-effectiveness of $100,000 to $150,000 per QALY gained, the reduction in price required was between 71% and 77%. It is important to note that within the Evidence Report, the Institute for Clinical and Economic Review adopted similar approaches to the manufacturer for modelling the continued treatment benefit in terms of $ppFEV_1$ decline and the dual benefit from LUM/IVA in terms of effects on exacerbation rates. It is noted that in both of these approaches, the assumptions are not supported by the clinical evidence available.

Patient Input

Two patient groups, Cystic Fibrosis Canada and the Cystic Fibrosis Treatment Society, provided patient input. Information was gathered from 408 individuals, who included adults living with CF and parents or caregivers of patients with CF.

The most significant clinical impact noted is in the lungs, where patients have difficulty in clearing secretions, which, in combination with aberrant inflammation, leads to persistent infections. This may cause progressive scarring of the airways and a progressive and sometimes rapid decline in lung function, leading to respiratory failure — the main cause of death in patients with CF. CF also affects the digestive system, so maintaining body weight can be challenging for patients affected by the disease. Lung function (through ppFEV1) and body weight were outcomes considered in the manufacturer's economic evaluation.

Patients also noted that acute infections and episodic exacerbations that frequently lead to hospitalizations have a significant impact on their day-to-day quality of life. These aspects were included, indirectly, within the manufacturer's economic evaluation. It was further noted that caregivers may also have to change their social activities and their employment in order to accommodate the treatment of a loved one with CF. The manufacturer did not collect information on caregivers in the clinical studies and considered the perspective of the public payer in its economic analysis.

Conclusions

The manufacturer estimated that the incremental cost per QALY gained for LUM/IVA for the treatment of CF in patients six years of age and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator gene was $446,529; as such, a price reduction in excess of 70% is required for LUM/IVA to lead to an ICER of $100,000 per QALY.

CDR found several major limitations with the manufacturer's submission, which suggested that the submitted result was heavily biased in favour of LUM/IVA. CDR reanalysis found that for patients older than 12, the incremental cost per QALY gained for LUM/IVA was $3.8 million. For patients aged between six and 11, the CDR base-case analysis estimated the incremental cost per QALY gained to be $7.3 million. For both patient groups, the CDR base case suggests that a price reduction of 97% is required for an ICER of $100,000.

Appendix 1: Cost Comparison

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 7: CADTH Common Drug Review Cost Comparison Table for Treatment of Cystic Fibrosis

Drug/Comparator	Strength	Dosage Form	Unit Cost ($)	Recommended Treatment Regimen	Average Daily Cost ($)	Average Annual Cost ($)
Lumacaftor/ ivacaftor (Orkambi)	**200 mg/ 125 mg**	**Tablet**	**170.5357[a]**	**400mg/250 mg every 12 hours**	**682.14**	**248,982**
Treatments Indicated for the Management of Cystic Fibrosis Patients						
Aztreonam (Cayston)	75 mg/vial	Inhaled solution	44.0700	Alternating 75 mg three times daily for 28 days, followed by 28 days off	132.21[b]	24,128[b]
Dornase alfa (Pulmozyme)	1 mg/mL (2.5 mL)	Inhaled solution	39.7500	2.5 mg once or twice daily	39.75 to 79.50	14,509 to 29,018
Ivacaftor (Kalydeco)	150 mg	Tablet	420.0000	150 mg twice daily	840.00	306,600
Levofloxacin (Quinsair)	240 mg/2.4 mL (100 mg/mL)	Inhalation solution	72.2346[c]	Alternating 240 mg twice daily for 28 days, followed by 28 days off	144.47[b]	26,366[b]
Tobramycin (generic)	300 mg/5 mL (60 mg/mL)	Inhaled solution (single-dose ampoule)	27.3900	Alternating 300 mg twice daily for 28 days, followed by 28 days off	54.78[b]	9,997[b]
Tobramycin (Tobi Podhaler)	28 mg	Inhalation capsule	13.4510	Four capsules (112 mg) twice daily for 28 days, followed by 28 days off	107.61[b]	19,638[b]

[a] Manufacturer's submitted price.
[b] Daily cost is for days of use, annual cost includes off days.
[c] CADTH Canadian Drug Expert Committee recommendation for Quinsair, November 2016.[22]
Source: Saskatchewan Formulary[21] unless otherwise indicated. Administration costs are not included.

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is LUM/IVA + SoC Relative to SoC Alone?

LUM/IVA + SoC vs. SoC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	The incremental cost per QALY gained (ICER) for LUM/IVA in patients aged six and over is $446,529 (manufacturer's analysis). The ICER for LUM/IVA in patients aged 12 and older is $3.8 million (CDR base-case analysis). The ICER for LUM/IVA in patients aged six to 11 is $7.3 million (CDR base-case analysis).					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; LUM/IVA = lumacaftor/ivacftor; N/A = not applicable; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	The model is unnecessarily complex, which makes it difficult to conduct the necessary troubleshooting. The use of macros to generate individual patient simulations lacks transparency and makes it impossible to validate the results. The run time to conduct the necessary probabilistic analysis is approximately two months.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 10: Authors’ Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☒ Other (please specify)

Unknown authors	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

No reports by other Health Technology Assessment agencies were found reviewing lumacaftor/ivacaftor (LUM/IVA) or the treatment of cystic fibrosis (CF) in patients six-years-old and older who are homozygous for the F508del mutation in a CF transmembrane conductance regulator (CFTR). The Pharmaceutical Benefits Advisory committee (PBAC, Australia) recently issued a positive recommendation for both doses of LUM/IVA under a managed access program; requesting that further data be collected to demonstrate that differences in the rate of decline in lung function and the amount of pulmonary exacerbations are sustained over a period of at least four years in actual clinical practice. No information regarding the cost-effectiveness was reported; however, the available documentation noted that the managed access program considered relevant subsidies based on the information collected by the manufacturer.[23] In addition to CADTH,[5] LUM/IVA has been reviewed for the same indication in patients 12-years and older by the Institute national d'excellence en santé et en services sociaux (INESSS, Quebec),[24] the National Institute for Health and Care Excellence (NICE, UK),[25] and PBAC.[26]

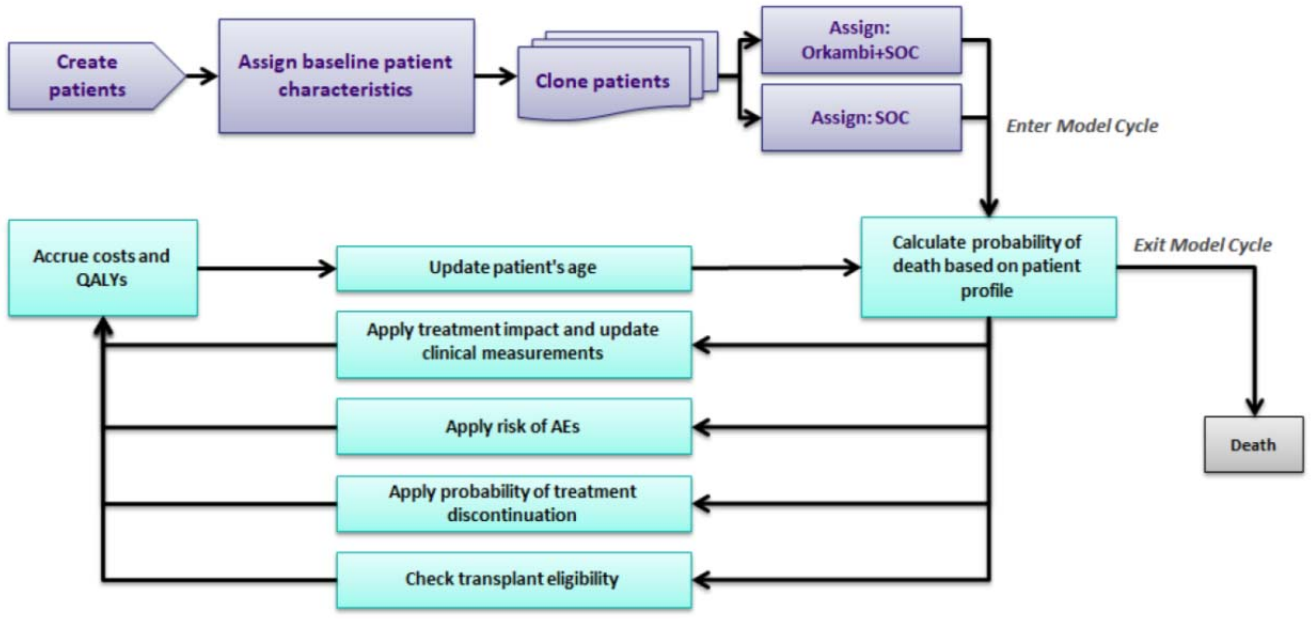
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

Individual patient simulation model (Figure 2):

- cohort of 6,000 patients simulated based on clinical trial patient populations
- primary estimates based on 1,000 replications of simulated patient cohort
- four-week cycle for first two years — annual thereafter
- in each cycle patient has risk of death derived from the Stephenson analysis of the Canadian cystic fibrosis (CF) cohort adjusted by the Liou predictive model (refs)
- EuroQol 5-Dimensions scores based on per cent predicted forced expiratory volume in one second ($ppFEV_1$) and exacerbations
- $ppFEV_1$ is updated each cycle based on treatment-specific estimates from the relevant clinical studies for the first 24 weeks and then assumed differential rates of decline thereafter
- exacerbations assumed a function of both $ppFEV_1$ and an independent treatment effect with lumacaftor/ivacftor (LUM/IVA)
- costs include costs of lumacaftor/ivacftor (LUM/IVA) for managing CF (which is assumed a function of $ppFEV_1$), costs of exacerbations, and costs of adverse events
- analysis incorporates the probability of lung transplantation and the associated costs and utilities.

Figure 2: Model Schematic



AEs = adverse events; QALYs = quality-adjusted life-year; SoC = standard of care.
Source: Manufacturer's pharmacoeconomic submission.[10]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
24 week impact on $ppFEV_1$	Clinical trials: • TRAFFIC and TRANSPORT studies for patients aged over 12[3,4] • 809-109 study for patients aged between six and 12[7]	Appropriate
$ppFEV_1$ beyond 24 weeks	For LUM/IVA: • 24-week extension data from PROGRESS for patients aged over 12[8,9] • opinion for patients aged between six and 12 For SoC: cohort studies	Inappropriate — see main report
Exacerbation rate as a function of $ppFEV_1$	Analysis of US CF Registry data	Possibly appropriate, though standard errors of coefficients not provided. Inappropriate for those aged between six and 11 as increase in exacerbations on LUM/IVA was found.
Additional incremental effect of LUM/IVA on exacerbations	Clinical trials: • TRAFFIC and TRANSPORT studies for patients aged 12 and older	Inappropriate — see main report
Lung transplantation probabilities, costs, and utilities	Canadian published data and provincial ministry data	Appropriate
Adverse event rates	Clinical trials	Appropriate
Costs data	Unpublished chart review for quantities of resource use Provincial ministry data Published studies	Unpublished data are hard to verify. Most differences based on $ppFEV_1$ are estimated through expert opinion not chart review. Costs sources appear appropriate but some are old.
Utility data	Unpublished poster presentation	Unpublished data are hard to verify, though methodology appears appropriate.

CF = cystic fibrosis; LUM/IVA = lumacaftor/ivacftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SoC = standard of care.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Cost of LUM/IVA will be reduced by 82% after 12 years. Inappropriate unless manufacturer willing to guarantee a price reduction.	Inappropriate. Biased to assume reduced costs but no reduced effectiveness.
$ppFEV_1$ will decline at a lower rate long term for LUM/IVA + SoC than SoC.	Unjustified given follow-up data are not randomized beyond 24 weeks and clinical trial data suggests parallel decline in $ppFEV_1$.
Assume dual effect of exacerbations through an indirect effect through $ppFEV_1$ and a direct effect.	Likely leading to double counting of benefit. Unjustified in patients aged between 6 and 11 as LUM/IVA-treated patients had higher exacerbation rates.

LUM/IVA = lumacaftor/ivacftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; SoC = standard of care.

Validation of the Manufacturer's Analysis

Validation of the Non-Bootstrap Approach

An approach taken was to assess whether a non-bootstrap approach to the analysis would give similar results to the submitted results from the manufacturer. In this approach, each patient profile is run through the model once with progression through random number generation.

While not ideal, the lack of transparency within the model with respect to the function of the probabilistic analysis and the extreme run time — in excess of 60 days — makes this a necessity. If results were more or less the same, the adoption of this approach would make the ability to conduct multiple reanalyses and a sufficient review feasible.

Initial results from the manufacturer with 6,000 random patient profiles and 1,000 iterations were:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
Life-years	24.48	18.98	5.51
QALYs	22.11	16.90	5.20
Total costs	$2,738,444	$414,422	$2,235,590
Cost per QALY gained			$446,529

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

CADTH Common Drug Review (CDR) reran the analysis with 6,000 random profiles and 100 iterations. This took in excess of 30 hours to run. The results were similar to the initial results:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
Life-years	24.30	17.79	5.51
QALYs	21.94	16.74	5.20
Total costs	$2,732,553	$419,803	$2,212,750
Cost per QALY gained			$444,864

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Results from the CDR reanalysis using a non-bootstrap approach were:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
Life-years	24.22	18.65	5.57
QALYs	21.89	16.62	5.27
Drug	$2,457,515	$0	$2,457,515
Total costs	$2,766,701	$407,372	$2,359,329
Cost per QALY gained			$447,691
Cost per life-year gained			$423,594

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Thus, CDR concluded that the non-bootstrap approach was appropriate given its rough equivalency to the manufacturer's submitted base probabilistic analysis results.

Verification of Results in the Population Aged 12 and Older

Before rerunning the CDR base case it was necessary to verify that the current model gives similar results to the model submitted for the previous submission relating to those aged 12 and older.

The manufacturer's base results for the previous submission obtained from the published pharmacoeconomic review report were:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
QALYs	11.33	7.79	3.54
Drug	$1,800,132	$0	$1,800,132
Total costs	$1,951,354	$233,012	$1,718,342
Cost per QALY gained			$485,767

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Source:[26]

The results for the CDR base-case analysis from the previous CDR pharmacoeconomic review report were:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
QALYs	7.55	7.13	0.42
Drug	$2,010,589	$0	$3,213,165
Total costs	$2,201,383	$206,063	$3,204,133
Cost per QALY gained			$4,773,615

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Source:[26]

CDR reanalysis of the manufacturer's model included in the current submission limited to patients aged 12 and older found similar cost-effectiveness ratios but different expected values from the previous submission:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
QALYs	18.62	13.94	4.68
Drug	$2,261,619	$0	$2,261,619
Total costs	$2,550,698	$364,736	$2,185,962
Cost per QALY gained			$467,109

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

On closer examination of the two submissions, CDR identified the following primary reasons for differences:

1. Initial submission used a 5% discount rate — current uses a 1.5% rate.
2. Different assumptions relating to change in $ppFEV_1$%:
   - assumed reduction in decline in $ppFEV_1$ on LUM/IVA + standard of care (SoC) in original submission was 71% for < 18 years and 72% for ≥ 18 years. In resubmission effect sizes were much lower and assumed 42% for all ages
   - in initial submission, the manufacturer assumed a single absolute decline in $ppFEV_1$ after 24 weeks on SoC for those aged ≥ 11; in current submission decline varies by age.
3. The two submissions adopted different baseline mortality with CF patients.

CDR was able to rerun the analyses with the original assumptions for the first and second points listed above but could not address the third. The results provided outcomes more in line with the previous submission:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
QALYs	11.74	8.73	3.01
Drug	$1,800,132	$0	$1,800,132
Total costs	$1,916,812	$235,588	$1,681,224
Cost per QALY gained			$558,291

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

CDR Reanalyses (of Current Submitted Model): Details

CADTH Common Drug Review's Base-Case Analysis for the Population Aged 12 and Older

Based on the above results, CDR proceeded to reanalyze the current submission restricted to patients aged 12 and older. CDR reanalysis was based on making the same amendments to the current submitted model as those identified in the previous CDR pharmacoeconomic review.

The following amendments to assumptions within the analysis were made:

- CDR adopted revised assumptions relating to the decline in ppFEV$_1$% over time using the same rate of decline with both LUM/IVA + SoC and SoC alone. The issue addressed was that the manufacturer's submission made the assumption that after the initial period represented by the clinical trial ppFEV$_1$% will decline. This appears reasonable, but the manufacturer assumes a differential rate of decline favouring LUM/IVA + SoC. This was not based on any long-term evidence; rather, short-term data from two distinct observational studies. A more acceptable assumption, which would still favour LUM/IVA + SoC (in that it advocates a continuous treatment effect rather than any potential treatment waning), would be to assume the same percentage decline.
- CDR used the full costs of LUM/ICA for the full-time horizon of the model. The manufacturer assumed that the cost of LUM/IVA would be reduced by 82% after 12 years due to generic equivalents being available. No justification for this assumption is provided and this is counter to CADTH guidance, which outlines that full costs for LUM/IVA for the time horizon of the model should be included.
- CDR assumed that LUM/IVA would have an impact on reducing exacerbation rates through reductions in ppFEV$_1$%. The manufacturer had made this assumption, which appears reasonable; however, the manufacturer assumed a differential rate of exacerbation with LUM/IVA + SoC after allowing for the effect of ppFEV$_1$%. This is obvious double counting and, to allow for a more reasonable assumption around the impact of LUM/IVA + SoC on exacerbations, the effect of ppFEV$_1$% in exacerbations was included but with no additional relative reduction.

The results for the CDR base-case analysis for those aged 12 and older using the model provided for the current submission are:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
QALYs	14.79	13.94	0.85
Drug	$3,213,165	$0	$3,213,165
Total costs	$3,568,869	$364,736	$3,204,133
Cost per QALY gained			$3,785,432

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Results differ slightly from the expected values from the previous pharmacoeconomic review report. This is likely due to both the use of a different discount rate in the previous submission and because the two submissions adopted different baseline mortality with CF patients.

CADTH Common Drug Review's Base-Case Analysis for the Six Year to 11 Year Old Population

Rerunning the manufacturers' submitted model using the non-bootstrap approach for those aged under 12 provides the following results:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
Life-years	37.09	28.67	8.42
QALYs	34.09	25.86	8.23
Drug	$3,072,672	$0	$3,072,672
Total costs	$3,468,243	$552,207	$2,916,036
Cost per QALY gained			$354,208
Cost per life-year gained			$346,421

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

On reviewing the current submission, CDR found the same weaknesses with the submitted analysis as with the submission for those aged 12 and older. Thus, the same amendments were made to the model:

- CDR adopted revised assumptions relating to the decline in ppFEV$_1$% over time using the same rate of decline with both LUM/IVA + SoC and SoC alone.
- CDR used the full costs of LUM/ICA for the full-time horizon of the model.
- CDR included the effect of ppFEV$_1$% in exacerbations but with no additional relative reduction. It should be clearly noted that the approach adopted by CDR in its reanalysis is still clearly an assumption favourable to LUM/IVA given that the rate ratio form the 809-109 pediatric efficacy trial was 1.33, suggesting a higher rate of exacerbation on LUM/IVA and not the lower-rate modelled.

The results for the CDR base-case analysis for those under 12 years old are:

Outcome	LUM/IVA + SoC	SoC	Incremental (LUM/IVA vs. SoC)
Life-years	29.51	28.67	0.84
QALYs	26.65	25.86	0.79
Drug	$5,775,150	$0	$5,775,150
Total costs	$6,307,190	$552,207	$5,754,983
Cost per QALY gained			$7,258,514
Cost per life-year gained			$6,879,650

LUM/IVA = lumacaftor/ivacftor; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Detailed Results of Limitations

The impact of each of the assumptions within the CADTH base case is detailed in Table 13.

Each of the changes affect the estimated incremental cost-effectiveness ratio to a modest extent but the combination of all three changes has a synergistic effect in increasing both the incremental costs and quality-adjusted life-years associated with LUM/IVA.

Table 13: Detailed Results of Individual Limitations — Population: 12 Years of Age and Older

Scenario	Costs		QALYs		Cost per QALY gained
	LUM/IVA + SoC	SoC	LUM/IVA + SoC	SoC	
CDR base case	$3,568,869	$364,736	14.79	13.94	$3,785,432
No increased benefit in $ppFEV_1$	$2,401,035	$364,736	16.08	13.94	$954,520
Full treatment costs	$4,553,906	$364,736	18.62	13.94	$895,165
No double counting of exacerbation benefit	$2,180,567	364,736	17.40	13.94	$631,018

CDR = CADTH Common Drug Review; LUM/IVA = lumacaftor/ivacftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; QALY = quality-adjusted life-year; SoC = standard of care.

In the six year to 11 year population the change with respect to exacerbations had limited impact as the model already had an assumption related to no incremental effect on exacerbations before the age of 12. The combination of the first two changes has a synergistic effect in increasing both the incremental costs and quality-adjusted life-years associated with LUM/IVA.

Table 14: Detailed Results of Individual Limitations Population: Six Years to 11 Years of Age

Scenario	Costs		QALYs		Cost per QALY gained
	LUM/IVA + SoC	SoC	LUM/IVA + SoC	SoC	
CDR base case	$6,307,190	$552,207	29.51	25.86	$7,258,514
No increased benefit in $ppFEV_1$	$2,652,256	$552,207	27.90	25.86	$1,298,999
Full treatment costs	$7.591,981	$552,207	34.09	25.86	$922,191
No double counting of exacerbation benefit	$2,979,555	$552,207	33.44	25.86	$393,176

LUM/IVA = lumacaftor/ivacftor; $ppFEV_1$ = per cent predicted forced expiratory volume in one second; QALY = quality-adjusted life-year; SoC = standard of care.

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