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CADTH Reimbursement Recommendation

Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta)

Indication: Treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Sponsor: Vertex Pharmaceuticals (Canada) Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Trikafta?

CADTH recommends that Trikafta be reimbursed by public drug plans for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least 1 F508del mutation in the *CFTR* gene if certain conditions are met.

Which Patients Are Eligible for Coverage?

Trikafta should be reimbursed for patients who have a percent predicted forced expiratory volume in 1 second ($ppFEV_1$) of 90% or less at the onset of Trikafta treatment.

What Are the Conditions for Reimbursement?

At least 1 of the following must be demonstrated after 6 months of treatment with Trikafta: an increase of at least 5% in $ppFEV_1$, a decrease in the number of pulmonary exacerbations or number of days that antibiotics needed to be taken for pulmonary exacerbations, a decrease in CF-related hospitalizations, no decline in BMI, or an improvement of at least 4 points in the CFQ-R respiratory domain scale. The price of Trikafta must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

Trikafta was associated with meaningful improvements in lung function, nutritional status, quality of life, and a reduced rate of pulmonary exacerbations for patients with at least 1 F508del mutation in the *CFTR* gene.

Reimbursement was recommended for patients with advanced lung disease (i.e., $ppFEV_1$ < 40%) for whom there is a significant need for treatment options and Trikafta may be of benefit. Reimbursement for Trikafta was not recommended in patients with normal lung function ($ppFEV_1$ > 90%) because of insufficient and low-quality evidence that did not show treatment benefit.

The price of Trikafta that was submitted to CADTH needs to be reduced by at least 90% for the treatment to be considered cost-effective at a $50,000 per quality-adjusted life-year (QALY) threshold.

Additional Information

What Is Cystic Fibrosis?

CF is a progressive, fatal, genetic disease that primarily affects the lungs and digestive system. Those living with CF lose the ability to breathe due to accumulated lung damage caused by chronic lung inflammation and infections.

Unmet Needs in Cystic Fibrosis

There are no treatments currently available that effectively meet the most important goals of CF therapy: prolong survival, prevent the need for lung transplantation, slow the decline in lung function over time, or reverse the course of the disease.

How Much Does Trikafta Cost?

Treatment with Trikafta is expected to cost $306,600 per patient per year (or $840 per day).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that elexacaftor, tezacaftor, and ivacaftor plus ivacaftor (ELX-TEZ-IVA) should be reimbursed for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Four double-blind randomized controlled trials (RCTs) demonstrated that treatment with ELX-TEZ-IVA resulted in added clinical benefit for patients who were heterozygous for the F508del mutation in the *CFTR* gene and who had 1 minimal function mutation (F/MF) (Study 102; N = 405), homozygous for the F508del mutation (F/F) (Study 103; N = 107 and Study 109; N = 107), and heterozygous for the F508del mutation and a residual function mutation (F/RF) or a gating mutation (F/G) (Study 104; N = 259). Study 102 demonstrated that, compared with placebo, 24 weeks of treatment with ELX-TEZ-IVA was associated with statistically significant and clinically meaningful improvements in lung function (increase in percent predicted forced expiratory volume in 1 second [$ppFEV_1$]), nutritional status (increase in body mass index [BMI]), health-related quality of life (increase in Cystic Fibrosis Questionnaire Revised [CFQ-R] respiratory domain scores) and a reduced rate of pulmonary exacerbations, including events that required IV antibiotics and/or hospitalization to manage. Study 103, Study 104, and Study 109 demonstrated that switching to ELX-TEZ-IVA after 4 weeks of treatment with either tezacaftor plus ivacaftor (TEZ-IVA) or IVA alone was associated with statistically significant and clinically meaningful improvements in $ppFEV_1$ and CFQ-R compared with remaining on the other *CFTR* modulators. Given all the evidence, CDEC concluded that ELX-TEZ-IVA met some of the needs identified by patients, such as reducing CF exacerbations, improving health-related quality of life, improving lung function, and improving digestive health allowing people to maintain a healthy body weight.

Based on the sponsor-submitted price for ELX-TEZ-IVA and the publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ELX-TEZ-IVA was $1,140,840 per quality-adjusted life-year (QALY) for the F/F genotype, $1,150,105 per QALY for the F/MF genotype, $1,911,977 per QALY for the F/RF genotype, and $1,067,215 for the F/G genotype compared with best supportive care. For the F/G genotype, ELX-TEZ-IVA was associated with an ICER $181,718 per QALY in comparison with IVA monotherapy. At these ICERs, ELX-TEZ-IVA is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for patients 12 years of age and older with CF who have at least 1 F508del mutation in the *CFTR* gene. A reduction in price of at least 90% is required for ELX-TEZ-IVA to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Confirmed diagnosis of CF with at least 1 F508del mutation in the *CFTR* gene	Treatment with ELX-TEZ-IVA demonstrated added clinical benefit for patients with at least 1 F508del mutation in the *CFTR* gene based on 4 RCTs in patients with F/F, F/MF, F/G, and F/RF genotypes.
2. Aged 12 years and older	The indication approved by Health Canada for ELX-TEZ-IVA is limited to patients who are at least 12 years of age.
3. $ppFEV_1 \leq 90\%$	All 4 RCTs for ELX-TEZ-IVA required and included patients with a $ppFEV_1$ of ≥ 40% to ≤ 90% at the time of screening. • A subset of patients was enrolled with a baseline $ppFEV_1 < 40\%$; post hoc subgroup analyses in Study 102 suggested that treatment with ELX-TEZ-IVA resulted in clinically meaningful improvements in the lung function of these patients. Patients with a $ppFEV_1 < 40\%$ represent a group with severe disease and significant unmet treatment needs. • There was insufficient data to evaluate the efficacy of ELX-TEZ-IVA in patients with a baseline $ppFEV_1 > 90\%$.
4. The following measurements must be completed before initiating treatment with ELX-TEZ-IVA: 4.1. baseline spirometry measurements of FEV_1 in litres and percent predicted (within the last 30 days) 4.2. number of days treated with oral and IV antibiotics for pulmonary exacerbations in the previous 6 months OR number of pulmonary exacerbations requiring oral and/or IV antibiotics in the previous 6 months 4.3. number of CF-related hospitalizations in the previous 6 months 4.4. weight, height, and BMI 4.5. CFQ-R respiratory domain score.	To establish baseline values to be used for renewal of reimbursement for treatment with ELX-TEZ-IVA.
5. Patients should be optimized with BSC for their CF at the time of initiation.	Consistent with the RCTs that were conducted with ELX-TEZ-IVA, patients should have their $ppFEV_1$ evaluated when their other treatments for CF have been optimized.
6. The maximum duration of initial reimbursement is for 6 months.	The treatment effects of ELX-TEZ-IVA were typically evaluated at 24-weeks (approximately 6 months) in the studies.

Reimbursement condition	Reason
Renewal	
7. For the first renewal, the physician must provide at least 1 of the following to demonstrate benefit after 6 months of treatment with ELX-TEZ-IVA: 7.1. improvement of lung function by 5% of predicted or more, relative to baseline (baseline lung function should be measured within a 3-month period before beginning treatment with ELX-TEZ-IVA) 7.2. a decrease in the total number of days for which the patient received treatment with oral and/or IV antibiotics for pulmonary exacerbations compared with the 6-month period before initiating treatment OR a decrease in the total number of pulmonary exacerbations requiring oral and/or IV antibiotics compared with the 6-month period before initiating treatment 7.3. decreased number of CF-related hospitalizations at 6 months compared with the 6-month period before initiating ELX/TEX/IVA treatment 7.4. no decline in BMI at 6 months compared with the baseline BMI assessment 7.5. improvement by 4 points or more in the CFQ-R respiratory domain scale.	The studies demonstrated that treatment with ELX-TEZ-IVA was associated with statistically significant and clinically meaningful improvements in lung function (improvement in $ppFEV_1$), nutritional status (increase in BMI), health-related quality of life (increase in CFQ-R respiratory domain scores), and a reduced rate of pulmonary exacerbations, including events that required IV antibiotics and/or hospitalization.
8. The physician must provide evidence of continuing benefit from treatment with ELX-TEZ-IVA for subsequent renewal of reimbursement. Subsequent renewals should be assessed annually.	ELX-TEZ-IVA is a high-cost treatment with significant budgetary implications for the public health system. Annual assessments will help ensure that the treatment is used for those who are benefiting from the therapy.
Discontinuation	
9. Patient has undergone lung transplantation.	Patients who had a solid organ transplantation were excluded from the main studies of ELX-TEZ-IVA, and Canadian clinical experts indicated that the treatment should be discontinued in patients who receive lung transplantation.
Prescribing	
10. Prescribing of ELX-TEZ-IVA and monitoring of treatment response should be limited to CF specialists.	Care for CF patients is complex and is managed through specialized CF clinics in Canada.
11. ELX-TEZ-IVA should not be reimbursed in combination with other *CFTR* modulators.	There is no evidence for the use of ELX-TEZ-IVA in combination with other available *CFTR* modulators. • ELX-TEZ-IVA is a combination product containing the same active components as Symdeko (TEZ-IVA) and Kalydeco (IVA). • IVA is also a component of Orkambi (LUM-IVA).

Reimbursement condition	Reason
Pricing	
12. A reduction in price.	The ICER for ELX-TEZ-IVA in comparison with BSC ranged from $1,067,215 to $1,911,977 per QALY, depending on the genotype. A price reduction of at least 90% for ELX-TEZ-IVA is required for all 4 genotypes for ELX-TEZ-IVA to be considered cost-effective at a $50,000 per QALY WTP threshold in comparison with BSC.

BMI = body mass index; BSC = best supportive care; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire Revised; CFTR = cystic fibrosis transmembrane conductance regulator; ELX = elexacaftor; F/F = homozygous for the F508del mutation; F/G = heterozygous for the F508del mutation and a gating mutation; F/MF = heterozygous for the F508del mutation and 1 minimal function mutation; F/RF = heterozygous for the F508del mutation and a residual function mutation; ICER = incremental cost-effectiveness ratio; IVA = ivacaftor; LUM = lumacaftor; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; RCT = randomized controlled trial; QALY = quality-adjusted life-year; TEZ = tezacaftor; WTP = willingness to pay.

Implementation Guidance

1. A clinically significant improvement in lung function ($ppFEV_1$) is typically 5% from baseline and is at least 4 points for health-related quality of life (measured with the CFQ-R). Validated thresholds for clinically relevant improvements in the frequency of exacerbations, total number of days in hospital for CF-related reasons, total number of days of treatment with oral and/or IV antibiotics for pulmonary exacerbations, and nutritional status were not identified. Clinical expert input indicated that the goal of therapy is to improve nutritional status (i.e., increase BMI into the healthy range for age and sex) and to reduce the frequency of exacerbations and related health care use (i.e., antibiotic use and hospitalization).
2. Patients enrolled in 3 studies (Study 103, Study 104, and Study 109) received treatment with TEZ-IVA or IVA alone during the 28-day active treatment run-in periods. Patients were subsequently randomized to receive ELX-TEZ-IVA or to remain on the active treatment administered during the run-in period. Therefore, this evidence is most relevant to patients switching *CFTR* modulator therapy. The evidence for patients who are treatment naive is from Study 102 and indirect treatment comparisons.
3. The CADTH re-analyses estimated the incremental budget impact of reimbursing ELX-TEZ-IVA to be $1,279,931,452 over 3 years, which CDEC considered a potential barrier to implementation.

Discussion Points

- CF is a rare and serious disease that is life-limiting. The F508del mutation in the *CFTR* gene is the most commonly observed mutation, which may cause a more severe form of CF.
- CDEC discussed the impact of CF on patients and their caregivers, noting the impact on health-related quality of life is particularly high; as the disease progresses, the limitations on daily activities grow and more time and effort are needed to manage the progressive and debilitating symptoms. In addition to experiencing a physical decline, people with CF can also suffer from psychological challenges, such as depression, anxiety, and hopelessness. Patient input highlighted the following expectations for new treatment for

CF: stop or slow the progression of disease, reduce the frequency of exacerbations, reduce or avoid the development of comorbidities and disease complications, improve digestive health (attain and maintain a healthy weight), provide longer life expectancy, avoid hospitalizations and reduce the need for invasive procedures, reduce the burden of daily therapy, improve quality of life (especially wellness, well-being, and the ability to contribute to society), and minimize side effects. Given this input and the available evidence, CDEC concluded that ELX-TEZ-IVA potentially meets some important unmet needs identified by patients.

- CDEC noted that the outcomes evaluated in the studies were clinically relevant and that statistical testing appropriately controlled for multiple comparisons, especially Study 102, which evaluated the most outcomes of interest for the review.
- The committee discussed that the evidence for patients with advanced lung disease (i.e., $ppFEV_1$ < 40%) is limited to post hoc subgroup analyses and observational studies. However, the magnitude of the treatment effect with ELX-TEZ-IVA was consistently clinically meaningful across the various analyses (mean absolute improvement in $ppFEV_1$ with ELX-TEZ-IVA ranged from 9% to approximately 19%).
- CDEC noted that patients with $ppFEV_1$ greater than 90% at screening were excluded from the clinical trials and were excluded from the sponsor-provided economic model because of the lack of data for these patients in the trials. Clinician input stated that this group of patients would be considered for treatment with ELX-TEZ-IVA in practice settings to preserve lung function. The clinicians also noted that this group of patients may have lung damage before their $ppFEV_1$ declines below 90%, and that treatment may improve other organ manifestations of CF. Similarly, patient group feedback emphasized the potential benefits of preserving lung function in individuals having a $ppFEV_1$ greater than 90% as well as the improving multi-organ effects of CF and the potential benefits of treating other body systems despite having a $ppFEV_1$ greater than 90%. The only evidence for patients with $ppFEV_1$ greater than 90% within the indicated population is limited to open-label, uncontrolled, interim analyses from ongoing observational studies that reported on a single end point (i.e., change from baseline in $ppFEV_1$). No statistical analyses were performed. Therefore, there is currently insufficient evidence to determine the magnitude of benefit of ELX-TEZ-IVA in patients with $ppFEV_1$ greater than 90%. CDEC highlighted the efficacy of ELX-TEZ-IVA for this population as an important evidence gap.
- Except for IVA, the comparators that were used in active-controlled studies and indirect comparisons are not currently reimbursed (TEZ-IVA) or are sparsely reimbursed (LUM-IVA) by the CADTH-participating drug programs.
- CDEC noted that the included studies enrolled patients who were at least 12 years of age at screening and that this is reflected in the indication that has been approved by Health Canada. Studies investigating the efficacy and safety of ELX-TEZ-IVA in children younger than 12 years of age are currently ongoing.
- CDEC discussed the variability in response to treatments with clinical experts. It was noted that those with more advanced disease may show smaller changes from baseline in commonly measured outcomes (e.g., $ppFEV_1$) but still experience clinically relevant improvements in other outcomes (i.e., health-related quality of life, frequency of exacerbations, total number of days in hospital for CF-related reasons, total number of days of treatment with oral and/or IV antibiotics for pulmonary exacerbations, and nutritional status).
- CDEC noted that the trials enrolled patients with stable disease, yet there was variation in the measurements of $ppFEV_1$ from screening to randomization. CDEC discussed with

clinical experts that although $ppFEV_1$ does not usually vary much for each patient over a shorter period of time, it would be prudent to take at least 2 measurements of $ppFEV_1$ to gain a more stable value before starting treatment with ELX-TEZ-IVA and at the time of assessment for the renewal of reimbursement.

- A key limitation of the reviewed studies was the relatively short duration of treatment and follow-up for a life-long condition. Two of the RCTs were 24 weeks long (Study 102 and Study 109), but the other 2 were only 4 weeks (Study 103) and 8 weeks (Study 104) in duration. Therefore, the durability of treatment effect as well as the longer-term balance between benefits and harms with ELX-TEZ-IVA are uncertain.
- The key safety concern observed with ELX-TEZ-IVA from the studies was liver toxicity. The product monograph states that treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended but may be considered when there is a clear medical need and when the benefits are expected to outweigh the risks. In such situations, the dose of ELX-TEZ-IVA should be reduced (detailed regimen in the product monograph). Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with ELX-TEZ-IVA.
- CDEC discussed the sponsor-provided indirect treatment comparison between ELX-TEZ-IVA and LUM/IVA for patients with an F/F genotype, and ELX-TEZ-IVA versus placebo for those with an F/F, F/G, or F/RF genotype. Other than Study 104 and Study 109, none of the trials used in the indirect comparisons had a run-in period, and the direction of any potential bias associated with the run-in period could not be determined. Also, randomization was stratified according to F/G or F/RF genotype in Study 104; however, randomization was not stratified according to whether or not the patient had an F508del mutation in other included studies comparing ELX-TEZ-IVA with IVA. Therefore, the selection of the F508del subgroup of patients in the placebo-controlled IVA trials would not have maintained randomization. The limitations with the indirect evidence precluded drawing concrete conclusions from the results.

Background

Trikafta consists of a fixed-dose combination tablet containing ELX 100 mg, TEZ 50 mg, and IVA 75 mg co-packaged with a tablet containing IVA 150 mg. ELX-TEZ-IVA is indicated for the treatment of CF in patients aged 12 years and older who have at least 1 F508del mutation in the *CFTR* gene. The recommended dose is 2 tablets of ELX-TEZ-IVA (ELX 100 mg, TEZ 50 mg, and IVA 75 mg) taken in the morning and 1 tablet of IVA (150 mg) taken in the evening, approximately 12 hours apart, with fat-containing food. Health Canada has not authorized an indication for use in children younger than 12 years of age.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- a review of 4 of RCTs (Study 102, Study 103, Study 104, and Study 109), 1 long-term extension phase study (Study 105), 1 indirect comparison submitted by the sponsor, 2 observational studies that evaluated the use of ELX-TEZ-IVA in patients with advanced lung

disease, 1 study that modelled the potential impact of ELX-TEZ-IVA on CF-related morbidity and mortality, and 2 descriptive analyses in patients with ppFEV$_1$ greater than 90% in a real-world setting

- patient perspectives gathered by 3 patient groups: Cystic Fibrosis Canada (CF Canada), the Canadian Cystic Fibrosis Treatment Society, and CF Get Loud
- input from 5 clinical specialists with expertise diagnosing and treating patients living with CF
- input from 3 clinician groups, including the Canadian Cystic Fibrosis Clinic Directors, Cystic Fibrosis Canada's Accelerating Clinical Trials Network, and the Toronto Adult CF Clinic
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call from CADTH for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Three patient groups, CF Canada, the Canadian Cystic Fibrosis Treatment Society, and CF Get Loud, responded to the call from CADTH for patient input. Information for the CF Canada submission was based on a cross-Canada survey of patients and caregivers that was circulated through CF clinics, email, and social media (1,455 respondents). Canadian CF Treatment Society gathered information through one-on-one and group discussions with individuals with CF, parents, caregivers, and treating physicians. CF Get Loud gathered information from a letter campaign that received 11,364 letters from Canadians, a town hall with CF experts and leaders, and from 20 Canadians who are currently receiving treatment with ELX-TEZ-IVA.

The patient groups emphasized that CF has tremendous impact on those living with the condition, their loved ones, and on society. The most significant clinical impact is in the lungs, where patients experience progressive scarring of their airways and a progressive decline in lung function. Patients may suffer from pulmonary exacerbations requiring weeks of hospitalization and IV antibiotics. Malnutrition is another consequence of CF, and those living with the condition are often underweight and may require a feeding tube for supplemental nutrition. Patients may also suffer from CF-related comorbidities, such as CF-related diabetes and CF-related liver disease. In addition to the decline of CF patients' physical health, many suffer from the unseen effects of CF. These include, but are not limited to, depression, anxiety, and hopelessness. The mental anguish caused by the ever-present awareness of one's mortality cannot be expressed in words and are difficult to quantify. Parents and caregivers have an overwhelming desire to do something to help their loved ones.

Managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. As the disease progresses, even more time and effort are needed to manage the progressive and debilitating symptoms. The condition has a significant impact on day-to-day quality of life of patients and caregivers, affecting life decisions that include education, career, travel, relationships, and family planning.

Patients with CF and their loved ones are seeking treatments that can change the trajectory of the disease and improve both life expectancy and quality of life. Improved outcomes include retaining or increasing lung function, improving digestive health, increasing energy levels, and minimizing symptoms of CF. Patients want to avoid hospital admissions, reduce the need for invasive medical procedures, and decrease the treatment burden of daily therapies. They also wish to avoid the adverse effects of therapies, such as osteoporosis, antimicrobial resistance, and CF-related diabetes or liver dysfunction.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Similar to the input from the patient groups, the clinical experts consulted by CADTH indicated that there are significant unmet therapeutic needs for patients living with CF. There are no treatments currently available that can meet the most important goals of therapy, including prolonging survival, preventing the need for lung transplantation, slowing the decline in lung function over time, or reversing the course of the disease. In addition, the clinical experts noted that the current standard treatments for CF are burdensome for patients and their caregivers.

The clinical experts anticipate that ELX-TEZ-IVA would be used as a preventive therapy with the goal of initiating treatment before the patient develops significant lung disease. The clinical experts noted that ELX-TEZ-IVA could be used with every patient who meets the Health Canada–approved indication, regardless of their current or past treatment regimens. In clinical practice, eligible patients would be identified based on their *CFTR* genotype; however, there is no practical method that could be used to predict who would be most likely to respond to ELX-TEZ-IVA. The patients who are most in need of treatment with ELX-TEZ-IVA include those with moderate to severe lung disease (e.g., $ppFEV_1 \leq 60\%$), those whose BMI is less than or equal to 20 kg/m^2, those with frequent pulmonary exacerbations, and those experiencing a rapid decline in FEV_1. However, it may be that all patients, including those with mild lung disease or who are pre-symptomatic, could benefit from treatment when considering the long-term outcomes and goal of preventing severe outcomes.

The clinical experts noted that the magnitude of improvement with ELX-TEZ-IVA is far greater than any other currently available treatments for CF (including all other *CFTR* modulators). ELX-TEZ-IVA would replace earlier *CFTR* modulators considered by the experts to be less effective (e.g., LUM-IVA [Orkambi] and TEZ-IVA [Symdeko]); patients currently receiving those drugs would likely be switched to ELX-TEZ-IVA.

The following end points are routinely assessed in Canadian clinical practice: FEV_1, nutrition and growth (e.g., BMI or BMI z score), hospital admissions and outpatient treatments for pulmonary exacerbations, and pulmonary exacerbation frequency per year. The magnitude of improvement in CF outcomes that would be considered clinically significant depends on the baseline status of the patient. After initiating treatment with ELX-TEZ-IVA, those with less severe disease or more advanced disease may show smaller changes from baseline in commonly measured end points, but still experience clinically relevant improvements (e.g., stabilization). An improvement in $ppFEV_1$ of at least 5% would typically be considered clinically meaningful for most patients in Canadian clinical practice. The experts noted that an increase in BMI should only be viewed as a goal of therapy if the patient is malnourished at the time of initiating therapy. Increasing the BMI of a patient who is in the normal range

or overweight may pose challenges and should not be viewed as a desirable outcome for evaluating the response to a treatment such as ELX-TEZ-IVA.

Treatment with ELX-TEZ-IVA would likely be interrupted or discontinued because of adverse events or progression to lung transplant. The most common adverse event that would result in discontinuation would be development of persistent liver enzyme abnormalities.

The clinical experts noted that ELX-TEZ-IVA should be prescribed and monitoring of treatment should be done by an adult or pediatric CF clinic.

Clinician Group Input

Three groups of clinicians responded to the call from CADTH for input: the Canadian Cystic Fibrosis Clinic Directors, Cystic Fibrosis Canada's Accelerating Clinical Trials Network, and the Toronto Adult CF Clinic. The input from the clinician groups identified the same unmet medical needs for CF patients and the potential place in therapy for ELX-TEZ-IVA as the clinical experts consulted by CADTH. Similar to the clinical experts consulted by CADTH, the clinician groups noted that the impact of ELX-TEZ-IVA has been dramatic and life-altering for the patients who have received the treatment through Health Canada's Special Access Programme, compassionate access mechanisms, or in clinical trials (including patients who have advanced lung disease).

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review processes. The following were identified as key factors that could impact the implementation of a CADTH recommendation for ELX-TEZ-IVA:

- potential need for objective criteria that can be used to evaluate response to treatment
- potential time points that should be used when evaluating the response to treatment
- advice on the use of ELX-TEZ-IVA in key patient populations that were excluded from the phase III studies.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

There were 4 double-blind, phase III RCTs included in the CADTH systematic review: 1 placebo-controlled trial conducted in patients who were heterozygous for the F508del mutation and who had 1 minimal function mutation (F/MF) (Study 102; N = 405), 2 active-controlled trials in patients who were homozygous for the F508del mutation (F/F) (Study 103; N = 107 and Study 109; N = 107), and 1 active-controlled trial in patients who were heterozygous for the F508del mutation and a residual function mutation (F/RF) or a gating mutation (F/G) (Study 104; N = 259).

The double-blind treatment periods were 24 weeks in Study 102 and Study 109, 8 weeks in Study 104, and 4 weeks in Study 103. Study 103, Study 104, and Study 109 all included a 28-day active treatment run-in period when all patients with either an F/F or F/RF genotype received treatment with TEZ-IVA plus IVA (Study 103, Study 109, and the F/RF subgroup of patients in Study 104) and patients with an F/G genotype received treatment with IVA (F/G subgroup of patients in Study 104). Patients were subsequently randomized to receive ELX-TEZ-IVA or to remain on the active treatment administered during the run-in period. All the studies included a screening phase (up to 28 days) and a safety follow-up phase (approximately 4 weeks or entry into an open-label extension phase study).

The inclusion and exclusion criteria for the included RCTs were similar except for the *CFTR* genotypes (i.e., F/MF, F/F, F/G, or F/RF). Patients were required to have stable CF disease in the opinion of the investigator and a $ppFEV_1$ of at least 40% and less than or equal to 90% at the time of screening. The trials excluded patients with a history of colonization with *Burkholderia cenocepacia*, *Burkholderia dolosa*, and/or *Mycobacterium abscessus*. Patients were also considered to be ineligible if they reported an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the first dose of the study drug. Patients with a history of solid organ or hematological transplantation were excluded, as were patients with abnormal laboratory values (e.g., hemoglobin < 10 g/dL or < 100 g/L), abnormal liver function, or abnormal renal function.

Efficacy Results

Patients With F/MF Genotype (Study 102)

Treatment with ELX-TEZ-IVA was associated with a statistically significant absolute increase from baseline in $ppFEV_1$ compared with placebo at 4 weeks (least squares mean difference [LSMD] = 13.8%; 95% confidence interval [CI], 12.1% to 15.4%; P < 0.0001) and 24 weeks (LSMD = 14.3%; 95% CI, 12.7% to 15.8%; P < 0.0001). Improvements in $ppFEV_1$ with ELX-TEZ-IVA were observed at the time of the first post-baseline assessment (i.e., day 15) and were higher at all time points throughout the study. Results for change from baseline in $ppFEV_1$ were generally consistent across all subgroup analyses, including those based on age (12 to < 18 years or ≥ 18 years) and $ppFEV_1$ at screening (< 70% or ≥ 70%). The sponsor conducted an additional post hoc subgroup analysis for the subset of patients with a $ppFEV_1$ below 40% at baseline (16 of 203 [7.9%] in the placebo group and 18 of 200 [9.0%] in the ELX-TEZ-IVA group), in which the absolute difference in $ppFEV_1$ with ELX-TEZ-IVA versus placebo was 15.2% (95% CI, 7.3% to 23.1%) at 4 weeks and 18.4% (95% CI, 11.5% to 25.3%) at 24 weeks.

Treatment with ELX-TEZ-IVA was associated with a lower rate of pulmonary exacerbations compared with placebo (rate ratio = 0.37; 95% CI, 0.25 to 0.55). Similarly, treatment with ELX-TEZ-IVA was associated with lower rates of pulmonary exacerbations requiring hospitalization (rate ratio = 0.29; 95% CI, 0.14 to 0.61) and pulmonary exacerbations requiring IV antibiotic therapy (rate ratio = 0.22; 95% CI, 0.11 to 0.43). Hazard ratios (HRs) favoured ELX-TEZ-IVA over placebo for time to first pulmonary exacerbation (HR = 0.34; 95% CI, 0.22 to 0.52), time to first pulmonary exacerbation requiring hospitalization (HR = 0.25; 95% CI, 0.11 to 0.58), and time to first pulmonary exacerbation requiring IV antibiotics (HR = 0.19; 95% CI, 0.09 to 0.39).

Treatment with ELX-TEZ-IVA was associated with a statistically significant improvement in BMI at 24 weeks compared with placebo (LSMD = 1.04 kg/m^2; 95% CI, 0.85 to 1.23; P < 0.0001). In patients younger than 20 years of age (n = 145), those treated with ELX-TEZ-

IVA demonstrated improvements in BMI z-scores compared with placebo (LSMD = 0.30; 95% CI, 0.17 to 0.43). Similarly, the ELX-TEZ-IVA group demonstrated greater improvement in body weight at 24 weeks compared with the placebo group (LSMD = 2.9 kg; 95% CI, 2.3 to 3.4).

Treatment with ELX-TEZ-IVA was associated with a statistically significant and clinically meaningful improvement in the CFQ-R respiratory domain score from baseline compared with placebo through 24 weeks (LSMD = 20.2; 95% CI, 17.5 to 23.0).

The ELX-TEZ-IVA group demonstrated statistically significant reductions in sweat chloride compared with the placebo group at 4 weeks (LSMD = −41.2 mmol/L; 95% CI, −44.0 to −38.5) and 24 weeks (LSMD = −41.8; 95% CI, −44.4 to −39.3).

The Treatment Satisfaction Questionnaire for Medication (TSQM) was included as an exploratory end point for patients between the ages of 12 years and 17 years. The difference in change from baseline favoured ELX-TEZ-IVA compared with placebo in the domains for global satisfaction (LSMD = 11.9; 95% CI, 1.8 to 22.0) and effectiveness (LSMD = 14.4; 95% CI, 3.5 to 25.4). The TSQM was not included as an end point in Study 109.

Patients With F/F Genotype (Study 103 and Study 109)

In Study 103, treatment with ELX-TEZ-IVA was associated with a statistically significant and clinically meaningful increase from baseline in $ppFEV_1$ compared with TEZ-IVA at 4 weeks (LSMD = 10.0%; 95% CI, 7.4% to 12.6%; P < 0.0001). Improvements in $ppFEV_1$ with ELX-TEZ-IVA were observed at the time of the first post-baseline assessment (i.e., day 15) and were higher at all time points throughout the study. The results for change from baseline in $ppFEV_1$ were generally consistent across all subgroup analyses. A post hoc subgroup analysis from Study 103 suggested that the magnitude of the observed treatment effect (LS mean = 7.8%; 95% CI, 4.8% to 10.8%) for *CFTR* modulator–experienced patients is less than that for *CFTR* modulator–naive patients (LS mean = 13.2%; 95% CI, 8.5% to 17.9%). In Study 109, treatment with ELX-TEZ-IVA was associated with a statistically significant absolute increase from baseline in $ppFEV_1$ compared with TEZ-IVA through 24 weeks (LSMD = 10.2%; 95% CI, 8.2% to 12.1%; P < 0.0001).

Pulmonary exacerbations were only captured as adverse events in Study 103 and Study 109. The percentage of patients with at least 1 pulmonary exacerbation was greater in the TEZ-IVA group compared with the ELX-TEZ-IVA group in both studies.

Compared with TEZ-IVA, treatment with ELX-TEZ-IVA was associated with improvements in BMI at 4 weeks in Study 103 (LSMD = 0.60 kg/m^2; 95% CI, 0.41 to 0.79) and body weight at 4 weeks (LSMD = 1.6 kg; 95% CI, 1.0 to 2.1). Changes from baseline in BMI and body weight were not investigated in Study 109.

Treatment with ELX-TEZ-IVA was associated with a statistically significant and clinically meaningful improvement in CFQ-R respiratory domain score from baseline compared with TEZ-IVA at 4 weeks in Study 103 (LSMD = 17.4; 95% CI, 11.8 to 23.0) and through 24 weeks in Study 109 (LSMD = 15.9; 95% CI, 11.7 to 20.1).

The ELX-TEZ-IVA group demonstrated statistically significant reductions in sweat chloride compared with the TEZ-IVA group at 4 weeks in Study 103 (LSMD = −45.1 mmol/L; 95% CI, −50.1 to −40.1) and through 24 weeks in Study 109 (LSMD = −42.8; 95% CI, −46.2 to −39.3; P < 0.0001).

The TSQM was included as an exploratory end point in Study 103 for patients between the ages of 12 years and 17 years. The ELX-TEZ-IVA group demonstrated improvements compared with the TEZ-IVA group in the domains for global satisfaction (LSMD = 11.9; 95% CI, 1.8 to 22.0) and effectiveness (LSMD = 14.4; 95% CI, 3.5 to 25.4). The TSQM was not included as an end point in Study 109.

Patients With F/G and F/RF Genotypes (Study 104)

Treatment with ELX-TEZ-IVA was associated with a statistically significant within-group improvement in $ppFEV_1$ through 8 weeks in Study 104 (LS mean change = 3.7%; 95% CI, 2.8% to 4.6%; P < 0.0001). Treatment with ELX-TEZ-IVA was associated with a statistically significant improvement in $ppFEV_1$ compared to the control group (LSMD = 3.5%; 95% CI, 2.2% to 4.7%; P < 0.0001). Subgroup analyses based on the comparator group (i.e., patient genotype) demonstrated absolute improvements in $ppFEV_1$ with ELX-TEZ-IVA versus IVA (LSMD = 5.8; 95% CI, 3.5 to 8.0) and versus TEZ-IVA (LSMD = 2.0; 95% CI, 0.5 to 3.4).

Pulmonary exacerbations were only captured as adverse events. Compared with the pooled control group (TEZ-IVA and IVA), fewer patients who were treated with ELX-TEZ-IVA reported at least 1 pulmonary exacerbation (10.3% versus 2.3%).

Mean BMI increased in both the pooled control group (LS mean = 0.16 kg/m^2; standard error [SE] = 0.06) and the ELX-TEZ-IVA group (LS mean = 0.28 kg/m^2; SE = 0.06) with no statistically significant difference between the groups (LSMD = 0.13 kg/m^2; 95% CI, −0.03 to 0.29).

The ELX-TEZ-IVA group demonstrated a statistically significant increase in CFQ-R respiratory domain score from baseline (LS mean within-group change = 10.3; 95% CI, 8.0 to 12.7; P < 0.0001). Treatment with ELX-TEZ-IVA also resulted in an increase in CFQ-R respiratory domain score compared with the pooled TEZ-IVA and IVA control group (LSMD = 8.7; 95% CI, 5.3 to 12.1; P < 0.0001). Subgroup analyses demonstrated similar effect sizes for ELX-TEZ-IVA compared with IVA in patients with an F/G genotype (LSMD = 8.9; 95% CI, 3.8 to 14.0; P = 0.0008) and for ELX-TEZ-IVA compared with TEZ-IVA in patients with an F/RF genotype (LSMD = 8.5; 95% CI, 4.0 to 13.1; P = 0.0003). No statistical analyses were performed for changes from baseline in the non-respiratory domains of the CFQ-R.

The ELX-TEZ-IVA group demonstrated a statistically significant decrease in sweat chloride from baseline (LS mean = −22.3 mmol/L; 95% CI, −24.5 to −20.2; P < 0.0001). Treatment with ELX-TEZ-IVA also resulted in a decrease in sweat chloride from baseline compared to the pooled control group (LSMD = −23.1 mmol/L; 95% CI, −26.1 to −20.1; P < 0.0001).

Harms Results

Patients With F/MF Genotype (Study 102)

The overall percentage of patients who experienced at least 1 adverse event was 96.0% in the placebo group and 93.1% in the ELX-TEZ-IVA group in Study 102. The percentage of patients who experienced at least 1 serious adverse event (SAE) was 20.9% in the placebo group and 17.3% in ELX-TEZ-IVA. Pulmonary exacerbations were the most-reported SAE and were more frequent in the placebo group compared with the ELX-TEZ-IVA group (17.9% versus 6.4%). There were few other SAEs that were reported for more than 1 patient in each treatment group. There were 2 withdrawals due to adverse events (WDAEs) reported in the ELX-TEZ-IVA group (1.0%) and none in the placebo group. The reasons for discontinuation from the ELX-TEZ-IVA group included portal hypertension (0.5.%) and rash (0.5%).

Patients With F/F Genotype (Study 103 and Study 109)

The overall percentage of patients who experienced at least 1 adverse event in Study 103 and Study 109 was 63.5% and 88.5%, respectively, in the TEZ-IVA groups compared with 58.2% and 92.0%, respectively, in the ELX-TEZ-IVA groups. In Study 109, the percentage of patients who experienced at least 1 SAE was 15.9% in the TEZ-IVA group compared with 5.7% in the ELX-TEZ-IVA group. The difference between the groups was due to a greater percentage of patients in the TEZ-IVA group who experienced a pulmonary exacerbation compared with the ELX-TEZ-IVA group (11.4% versus 1.1%). SAEs were rare in the 4-week Study 103; SAEs were only reported for 1 patient (1.9%) in the TEZ-IVA group (pulmonary exacerbation) and 2 patients (3.6%) in the ELX-TEZ-IVA group (pulmonary exacerbation and rash). There were no WDAEs reported in either the TEZ-IVA or ELX-TEZ-IVA groups in Study 103. In Study 109, WDAEs were reported for 2 patients (2.3%) in the TEZ-IVA group (compulsive disorder and psychotic disorder) and 1 patient (1.1%) in the ELX-TEZ-IVA group (anxiety and depression).

Patients With F/G and F/RF Genotypes (Study 104)

The overall percentage of patients who experienced at least 1 adverse event was 66.7% in the ELX-TEZ-IVA group and 65.9% in the control group. The percentage of patients who experienced at least 1 SAE was 8.7% in the control group compared with 3.8% in the ELX-TEZ-IVA group. The difference between the groups was due to a greater percentage of patients in the control group who experienced a pulmonary exacerbation that was classified as an SAE compared with the ELX-TEZ-IVA group (5.6% versus 1.5%). There were 2 WDAEs in the control group (1.6%; pulmonary exacerbation, and anxiety and depression) and 1 in the ELX-TEZ-IVA group (0.8%; elevated alanine transaminase [ALT] and aspartate transaminase [AST] levels).

Critical Appraisal

Randomization was stratified based on relevant prognostic factors (i.e., age, sex, baseline ppFEV$_1$, and prior *CFTR* modulator use [in Study 104]). Baseline and demographic characteristics were generally well-balanced across the treatment groups in each of the included studies. Study treatments were administered in a double-blind manner with all groups issued the same number of tablets each day. The adverse event profile of ELX-TEZ-IVA and the comparators was unlikely to compromise blinding in any of the included trials. There were few patients who discontinued the trials (completion rate ranged from 96.8% to 100%); however, the studies were relatively short in duration, which may in part explain the high percentage of patients who completed the trials. Adherence with the study treatments was reported to be greater than 99% across all treatment groups in the included trials. In accordance with the study protocols, the use of concomitant medications remained stable throughout the treatment period for all treatment groups. The only exceptions were the lower usage of some antibiotics for pulmonary exacerbations in the ELX-TEZ-IVA group relative to the placebo group in Study 102 (this difference was attributable to the efficacy of ELX-TEZ-IVA for reducing pulmonary exacerbations relative to placebo). The primary and key secondary end points were analyzed with statistical testing procedures that controlled the type I error rate, and all end points within the statistical testing hierarchies were statistically significant.

The diagnostic criteria used in Study 103 and Study 109 were consistent with Canadian clinical practice for identifying patients with CF who are homozygous for the F508del-*CFTR* mutation. The gating and residual function mutations that were used to select patients for inclusion in Study 104 were consistent with the approved indications for TEZ-IVA and IVA in Canada. There were no widely accepted criteria for defining minimal function mutations in the *CFTR* gene; therefore, the identification of patients with minimal function mutations in Study

102 relied on a novel approach designed by the sponsor (i.e., in vitro response to TEZ, IVA, or TEZ-IVA). The clinical experts consulted by CADTH noted that terms *residual function* and *minimal function* are not currently used in Canadian clinical practice. Patients with CF with more severe lung disease (e.g., ppFEV$_1$ < 40% at screening) or a normal ppFEV$_1$ at screening (≥ 90%) were excluded from the studies; therefore, the results of the included studies are primarily applicable to patients with moderate (i.e., FEV$_1$ = 40% to 69%) to mild (i.e., FEV$_1$ = 70% to 89%) lung disease. As patients with advanced lung disease are an important subgroup with a high level of unmet medical need, CADTH supplemented this review with additional evidence from observational studies to address this important gap in the RCT evidence.

Study 103, Study 104, and Study 109 included an open-label, 4-week active treatment period with TEZ-IVA or IVA before randomization. Therefore, these trials were investigating switching to ELX-TEZ-IVA from either TEZ-IVA or IVA compared with remaining on TEZ-IVA for patients with an F/F or F/RF genotype or remaining on IVA for patients with an F/G genotype. Because TEZ-IVA is not widely reimbursed in Canada, the switching design limits the generalizability of the studies directly to the Canadian setting. To address this potential gap in the evidence, the sponsor submitted indirect comparisons with CADTH to provide an estimate of ELX-TEZ-IVA versus placebo for those with an F/F or F/RF genotype.

Indirect Comparisons

Description of Studies

Given the absence of RCTs, the sponsor conducted indirect comparisons to derive relative estimates of the clinical efficacy for ELX-TEZ-IVA compared with local standard of care in the F/F, F/RF, and F/G populations. Although head-to-head trials were conducted for ELX-TEZ-IVA versus TEZ-IVA (for patients with F/F or F/RF genotypes) and IVA (for patients with an F/G genotype), the sponsor conducted indirect comparisons to derive estimates of effect for ELX-TEZ-IVA versus LUM/IVA for patients with an F/F genotype and ELX-TEZ-IVA versus placebo for those with an F/F, F/G, or F/RF genotype. A literature search conducted by CADTH did not identify any additional published indirect comparisons that included the patients, interventions, and outcomes identified in the protocol for the CADTH review of ELX-TEZ-IVA.

All the sponsor's indirect comparisons were conducted using the Bucher method for continuous end points. The sponsor stated that the Bucher method was considered the most appropriate approach for these indirect comparisons because of the 4-week active treatment run-in periods in the ELX-TEZ-IVA trials. Because all the studies for TEZ-IVA, LUM/IVA, and IVA enrolled patients who were naive to *CFTR* modulator treatment, the baselines were not considered to be sufficiently comparable to the ELX-TEZ-IVA studies to conduct an individual patient data meta-analysis.

Efficacy Results

For patients with an F/F genotype, indirect comparisons were performed for ELX-TEZ-IVA versus placebo and ELX-TEZ-IVA versus LUM-IVA. The direct evidence for ELX-TEZ-IVA versus TEZ-IVA was from Study 104, the direct estimate for TEZ-IVA versus placebo was from the EVOLVE trial, and the direct estimate for LUM-IVA versus placebo was derived from a meta-analysis of the TRAFFIC and TRANSPORT trials. The sponsor reported the following indirect estimates of effect for ELX-TEZ-IVA compared with placebo for absolute change from baseline through 24 weeks: [redacted] for ppFEV$_1$, [redacted] for BMI, and [redacted] for the CFQ-R respiratory domain.

For patients with an F/G genotype, indirect comparisons were performed for ELX-TEZ-IVA versus placebo. The direct evidence for ELX-TEZ-IVA versus IVA was derived from a subgroup analysis of Study 104 and the estimates for IVA versus placebo were derived from a meta-analysis of subgroup data from 3 studies: STRIVE, KONNECTION, and KONDUCT. The sponsor reported the following indirect estimates of effect for ELX-TEZ-IVA compared with placebo for absolute change from baseline through 8 weeks: [redacted] for $ppFEV_1$, [redacted] for BMI, and [redacted] for the CFQ-R respiratory domain.

For patients with an F/RF genotype, indirect comparisons were performed for ELX-TEZ-IVA versus placebo. The direct evidence for ELX-TEZ-IVA versus TEZ-IVA was derived from a subgroup analysis of Study 104; the estimates for TEZ-IVA versus placebo were from the EXPAND trial. The sponsor reported the following indirect estimates of effect for ELX-TEZ-IVA compared with placebo for absolute change from baseline through 8 weeks: [redacted] for $ppFEV_1$, [redacted] for BMI, and [redacted] for the CFQ-R respiratory domain.

Harms Results

The indirect comparison filed by the sponsor did not include any comparisons for adverse events.

Critical Appraisal

The primary limitation of the indirect comparisons was the difference in study design across the included studies. The ELX-TEZ-IVA studies (i.e., Study 104 and Study 109) included an open-label, 4-week active treatment period with TEZ-IVA or IVA before randomization. None of the other trials used in the indirect comparisons had a similar run-in period; therefore, the study designs, baseline values, and the end point values for the common comparator were different. Because both the ELX-TEZ-IVA and the comparator groups of Study 104 and Study 109 received 4 weeks of treatment with a *CFTR* modulator, the direction of any potential bias associated with the run-in period is uncertain.

Other Relevant Evidence

Long-Term Extension Study

Study 105 is an ongoing, open-label, uncontrolled trial that enrolled patients who had completed Study 102 or Study 103 (i.e., patients with either an F/MF or an F/F genotype). Interim results were reported for 24 weeks of follow-up for Study 102 patients and 36 weeks for Study 103 patients (data cut-off: October 2019). A total of 507 patients were enrolled in the extension study (n = 400 from Study 102 and n = 107 from Study 103).

Efficacy Results

Among patients previously enrolled in Study 102, the absolute change from baseline to week 24 in $ppFEV_1$ was similar for patients who switched from placebo to ELX-TEZ-IVA (14.9%; 95% CI, 13.5% to 16.3%) and for those who remained on ELX-TEZ-IVA (14.3%; 95% CI, 12.9% to 15.7%) during the extension study. Patients previously enrolled in Study 103 reported an absolute change from baseline to week 36 in $ppFEV_1$ of 12.8% (95% CI, 10.1% to 15.4%) and 11.9% (95% CI, 9.3% to 14.5%) during the extension study for patients previously treated with TEZ-IVA and ELX-TEZ-IVA, respectively.

During treatment with ELX-TEZ-IVA, the annual event rate for pulmonary exacerbations was 0.27 (95% CI, 0.19 to 0.39) for those previously treated with placebo and 0.32 (95% CI, 0.24

to 0.44) for those previously treated with ELX-TEZ-IVA in Study 102 and 0.30 (95% CI, 0.20 to 0.45) for those previously enrolled in Study 103.

The LS mean change from baseline to week 24 for the CFQ-R respiratory domain was 19.2 (95% CI, 16.7 to 21.7) for those who switched from placebo to ELX-TEZ-IVA (Study 102) and 20.1 (95% CI, 17.6 to 22.6) for those who received ongoing ELX-TEZ-IVA treatment. In Study 103, the LS mean change was 13.8 (95% CI, 8.9 to 18.8) for those patients who were switched from TEZ-IVA to ELX-TEZ-IVA and 14.3 (95% CI, 9.5 to 19.2) for those treated with ELX-TEZ-IVA in both study periods.

The absolute change in BMI from baseline to week 24 (Study 102) or week 36 (Study 103) ranged from an LS mean of 1.2 kg/m^2 to 1.3 kg/m^2. The change from baseline in BMI z score was reported for patients who were 20 years of age or younger at the start of the parent studies. The point estimate for the LS mean change from baseline in z-scores ranged from 0.30 to 0.43 across the different treatment populations.

Harms Results

Most patients (93%) reported at least 1 adverse event during the extension study. The most-reported adverse events were infective pulmonary exacerbation of CF (25%), cough (23%), oropharyngeal pain (15%), and nasopharyngitis (14%). Seven patients (1.4%) stopped treatment due to adverse events, and 80 patients (16%) experienced at least 1 SAE.

Critical Appraisal

Study 105 is an ongoing, uncontrolled, open-label trial that enrolled patients who had completed Study 102 or Study 103. This was an unblinded study; therefore, patient's expectations of treatment could have potentially biased the reporting of subjective outcomes, such as respiratory symptoms (as measured by the CFQ-R) or harms. Extension studies are often limited by selection bias because only patients who are tolerant to treatment and complete the parent studies are eligible to enroll. For Study 105, the risk of selection bias may be low given that only [redacted] patients ([redacted]%) out of the [redacted] randomized in the parent studies were not enrolled or treated in the extension study. During the first 24 weeks of follow-up, discontinuation of treatment was also low ([redacted] patients, [redacted]%); however, the frequency of missing data was higher for some outcomes relative to others. Issues with the generalizability of these data are the same as for the parent double-blind studies.

Observational Studies in Patients With Advanced Lung Disease

Two observational studies provided short-term data on the efficacy and safety of ELX-TEZ-IVA in patients with CF who had advanced pulmonary disease ($ppFEV_1$ < 40% or under evaluation for lung transplantation). All patients had at least 1 F508del *CFTR* mutation.

Irish Cohort

The retrospective chart review by O'Shea et al. (2021) reported data for 14 patients who were followed for a mean duration of 4.9 months after starting ELX-TEZ-IVA. Statistically significant improvements were reported for mean $ppFEV_1$ (increased from 27% [SD = 7.3] at baseline to 36% [SD = 16.5] after a mean follow-up of 26 days); mean BMI (increased from 20.7 kg/m^2 [SD = 3.6] to 22.1 kg/m^2 [SD = 3.4]) and mean sweat chloride (reduced from 105 mmol/L [SD = 15] to 54 mmol/L [SD = 23]) after an average of 62 days of follow-up. The rate of infective pulmonary exacerbations requiring hospitalization was 0.28 events per month (SD = 0.17) in the 12 months before ELX-TEZ-IVA, and 0.04 events per month (SD = 0.07) during the 4.9-month follow-up period (P < 0.001).

French Cohort

The prospective cohort study by Burgel et al. (2021) reported data for 245 patients who were followed for a median of 84 days after initiating treatment with ELX-TEZ-IVA. The mean change from baseline in the $ppFEV_1$ was 15.1% (95% CI, 13.8% to 16.4%) and the change from baseline in weight was 4.2 kg (95% CI, 3.9 to 4.6), based on pooled data from assessments at 1 month and 3 months. The authors reported statistically significant reductions in the percentage of patients receiving long-term oxygen (43% at baseline versus 23% at 3 months), non-invasive ventilation (28% at baseline versus 20% at 3 months), and enteral tube feeding (18% at baseline versus 10% at 3 months). Data were missing for 31% of patients at the 3-month visits, with no imputation in the analyses. Prior to the initiation of ELX-TEZ-IVA, 16 patients were waiting for a lung transplant and 37 were under consideration for inclusion as transplant candidates in the next 3 months (total = 53 patients; 22%). At the end of follow-up, 5 patients (2%) were on the transplant list or being considered for transplant, 2 patients had received a transplant (0.8%), and 1 patient died while waiting for transplant (0.4%).

Critical Appraisal

The 2 observational studies provided descriptive data on the effects of ELX-TEZ-IVA in CF patients with advanced lung disease. The short-term results showed acute increases in $ppFEV_1$ and weight that were comparable to those observed in the clinical trials, but these should be interpreted with caution given the limitations of the open-label, uncontrolled, observational study designs and the small sample size for the Irish cohort (N = 14). Both studies had a limited follow-up duration, and the monitoring and reporting of patient outcomes were impacted by the COVID-19 pandemic and lockdown measures. The large amount of missing data for some outcomes makes it challenging to interpret and generalize the results of these studies.

Simulation Study for Morbidity and Mortality

Stanojevic et al. (2020) used a microsimulation model to estimate the impact of treatment with ELX-TEZ-IVA in eligible patients in Canada. The model forecasted an increase in median survival and a reduction in pulmonary exacerbations with the introduction of ELX-TEZ-IVA. The outcomes from these simulations are contingent on the validity of several assumptions that were required to build the model and extrapolate the impacts out to 10 years. There is uncertainty in the extrapolation of the short-term effects of ELX-TEZ-IVA in a subset of patients with CF to the broader population in the longer term, and in the generalizability of observational data with IVA on the rate of decline in $ppFEV_1$ to patients treated with ELX-TEZ-IVA. Moreover, the model likely overestimates the proportion of CF patients who may receive ELX-TEZ-IVA and the impact of treatment on pulmonary exacerbations.

Observational Studies in Patients With $ppFEV_1$ Greater Than 90%

[redacted]. This information was filed with CADTH during the reconsideration phase and was considered by CDEC as part of their deliberations. [redacted]

Interim Analysis From the HELIO Study

HELIO is an ongoing multi-centre, prospective, observational study conducted in the US to evaluate the clinical effectiveness of ELX-TEZ-IVA in a real-world setting (N = approximately

200). The study will compare data from a 12-month period before initiating treatment with ELX-TEZ-IVA with data after 16 months of treatment with ELX-TEZ-IVA. [redacted]

US Cystic Fibrosis Foundation Patient Registry

[redacted]

Table 2: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation
Target population	Patients with CF aged 12 years and older who have at least 1 F508del mutation in the *CFTR* gene, represented by the following 4 genotypes considered in separate analyses: 1. Homozygous for F508del-*CFTR* (F/F) 2. Heterozygous for F508del-*CFTR* with a minimal function mutation (F/MF) 3. Heterozygous for F508del-*CFTR* with a residual mutation (F/RF) 4. Heterozygous for F508del-*CFTR* with a gating mutation (F/G), inclusive of R117H
Treatment	ELX-TEZ-IVA, with background BSC
Submitted drug price	Elexacaftor-tezacaftor-ivacaftor and ivacaftor (Trikafta), 100 mg-50 mg-75 mg and one 50 mg tablets: $280 per tablet, $840 per daily dose
Annual cost	At the recommended dose of 2 tablets of ELX 100 mg-TEZ 50 mg-IVA 75 mg taken in the morning and 1 tablet of IVA 150 mg taken in the evening, the annual cost is $306,600 per patient (or $840 daily).
Comparators	BSC for all genotypes, consisting of recommended medications (such as mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, and corticosteroids) and physiotherapy. Ivacaftor in patients heterozygous for F508del-*CFTR* with a gating mutation or the R117H mutation on the second allele in combination with BSC.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (approximately 65 years)

Component	Description
Key data sources	• A number of trials in *CFTR* modulator–naive patients to inform baseline patient characteristics for each genotype. • Literature to determine the impact of patient characteristics on mortality and the baseline rates of pulmonary exacerbations. • The sponsor commissioned multiple ITCs to inform placebo-adjusted rates for acute change in $ppFEV_1$ and mean change in weight-for-age z score for each genotype from baseline for patients on *CFTR* modulators with the F/F, F/RF and F/G genotypes. Study 102 was used to directly inform these values in the F/MF genotype. Patients on BSC were assumed to not experience any increase in either outcome. • Impact of treatment on long-term reduction in $ppFEV_1$ decline was based on non-comparative literature and not specific to ELX-TEZ-IVA. Impact of *CFTR* modulator use on pulmonary exacerbations beyond the influences of changes in $ppFEV_1$ to pulmonary exacerbation rates was based on an adjustment factor calculated by the sponsor.
Submitted results	1. Homozygous for F508del-*CFTR* (F/F) • ICER vs. BSC = $358,763 per QALY (incremental costs: $4,638,324; incremental QALYs: 12.93) 2. Heterozygous for F508del-*CFTR* with an MF mutation (F/MF) • ICER vs. BSC = $358,597 per QALY (incremental costs: $4,526,116; incremental QALYs: 12.59) 3. Heterozygous for F508del-*CFTR* with an RF mutation (F/RF) • ICER vs. BSC = $531,195 per QALY (incremental costs: $3,782,240; incremental QALYs: 7.12) 4. Heterozygous for F508del-*CFTR* with a gating mutation (F/G), inclusive of R117H • ICER vs. BSC = $353,239 per QALY (incremental costs: $4,184,761; incremental QALYs: 11.85) • ICER vs. IVA = $256,956 per QALY (incremental costs: $1,082,149; incremental QALYs: 4.21)
Key limitations	• There is no evidence on the long-term impact of ELX-TEZ-IVA on the rate of decline in $ppFEV_1$ or on pulmonary exacerbations in comparison with BSC or IVA. This leads to substantial uncertainty about the cost-effectiveness of ELX-TEZ-IVA. • There is uncertainty associated with the magnitude of benefit with ELX-TEZ-IVA for acute increases in $ppFEV_1$ and weight-for-age z score as determined by the sponsor-submitted ITC because there were key differences in the designs of the ELX-TEZ-IVA trials included in the ITC. • The sponsor incorporated dynamic pricing of ELX-TEZ-IVA based on an assumption of generic entry. This assumption is associated with considerable uncertainty and likely underestimates the total costs associated with ELX-TEZ-IVA. • Drug acquisition costs were adjusted for patient compliance, whereas treatment efficacy was not. Although drug wastage may occur, the drugs would be dispensed and paid for by public drug plans. This underestimated the total drug costs associated with ELX-TEZ-IVA. • Health care costs incurred by the health care system for the period for which ELX-TEZ-IVA is associated with a survival benefit in comparison with BSC were excluded, which underestimates the total costs associated with ELX-TEZ-IVA. • The sponsor included a treatment-specific utility increment to account for the effect of treatment with ELX-TEZ-IVA beyond that mediated via $ppFEV_1$ and pulmonary exacerbations. The increment calculated by the sponsor was adjusted for $ppFEV_1$ but not for pulmonary exacerbations, which likely leads to double counting of benefits with ELX-TEZ-IVA.

Component	Description
CADTH reanalysis results	CADTH conducted re-analyses which included the removal of an additional benefit of ELX-TEZ-IVA on the long-term rate of decline in $ppFEV_1$ and pulmonary exacerbations, the removal of dynamic pricing of ELX-TEZ-IVA, the inclusion of costs for ELX-TEZ-IVA in the period for which it achieved a survival benefit in comparison with BSC, the removal of an adjustment to drug acquisition costs by patient compliance, and the removal of a treatment-specific utility increment for patients on ELX-TEZ-IVA. 1. Homozygous for F508del-*CFTR* (F/F) • ICER vs. BSC = $1,140,840 per QALY 2. Heterozygous for F508del-*CFTR* with an MF mutation (F/MF) • ICER vs. BSC = $1,150,105 per QALY 3. Heterozygous for F508del-*CFTR* with an RF mutation (F/RF) • ICER vs. BSC = $1,911,977 per QALY 4. Heterozygous for F508del-*CFTR* with a gating mutation (F/G), inclusive of R117H • ICER vs. BSC = $1,067,215 per QALY • ICER vs. IVA = $181,718 per QALY ELX-TEZ-IVA was not cost-effective at a willingness-to-pay threshold of $50,000 per QALY in any scenario conducted by CADTH. A price reduction in excess of 90% for ELX-TEZ-IVA is required for all 4 genotypes for ELX-TEZ-IVA to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY in comparison with BSC.

BSC = best supportive care; CF = cystic fibrosis; ELX = elexacaftor; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; IVA = ivacaftor; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; QALY = quality-adjusted life-year; TEZ = tezacaftor; vs. = versus.

Budget Impact

CADTH identified key limitations with the sponsor's analysis: the anticipated market uptake of ELX-TEZ-IVA was substantially underestimated; drug acquisition costs were adjusted by patient compliance, which is not appropriate; several assumptions about patients eligible for IVA and the likelihood of switching did not align with expectations; and there was uncertainty with the proportion of patients who would be eligible for public coverage of ELX-TEZ-IVA. The CADTH re-analyses included increasing the market uptake of ELX-TEZ-IVA in all 3 years of the time horizon, removing the adjustment of costs for patient compliance, altering the proportion of patients currently receiving IVA to align with the submitted pharmacoeconomic model, and assuming a proportion of patients eligible for IVA but who were not receiving it would elect to receive ELX-TEZ-IVA. Based on the CADTH re-analyses, the budget impact of introducing ELX-TEZ-IVA is expected to be $419,553,709 in year 1, $426,604,322 in year 2, and $433,773,421 in year 3, for a 3-year total budget impact of $1,279,931,452. The model is sensitive to the proportion of patients eligible for public drug coverage and the anticipated market uptake and price of ELX-TEZ-IVA. Uncertainty remains about the proportion of patients with public drug coverage who would be eligible for ELX-TEZ-IVA. Changes in this parameter would lead to substantial changes in the estimated budget impact.

Members of the Canadian Drug Expert Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Initial meeting date: June 16, 2021

Regrets: One member did not attend.

Conflicts of interest: None

Reconsideration meeting date: August 18, 2021

Regrets: One member did not attend.

Conflicts of interest: None