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CADTH Reimbursement Recommendation

Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta)

Indication: Treatment of cystic fibrosis in patients aged 6 years and older who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator gene

Sponsor: Vertex Pharmaceuticals (Canada) Inc.

Final recommendation: Reimburse with conditions

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug dated September 16, 2021.

CADTH

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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 should be reimbursed by public drug plans for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least 1 F508del mutation in the *CFTR* gene if certain conditions are met.

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 percent predicted forced expiratory volume in 1 second ($ppFEV_1$), a decrease in the number of pulmonary exacerbations or number of days that antibiotics are needed to be taken for pulmonary exacerbations, a decrease in CF-related hospitalizations, no decline in body mass index, or an improvement of at least 4 points in the Cystic Fibrosis Questionnaire-Revised 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.

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 threshold.

Additional Information

What Is Cystic Fibrosis?

CF is a progressive, fatal, genetic disease that primarily affects the lungs and digestive system. Individuals living with CF lose the ability to breathe due to accumulated lung damage caused by chronic lung infections and inflammation. F508del is the most common mutation in the *CFTR* gene that results in CF.

Unmet Needs in Cystic Fibrosis

There are significant unmet therapeutic needs for individuals living with CF. 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 $306,810 per patient per year (or $840 per day).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that elexacaftor-tezacaftor-ivacaftor and ivacaftor (ELX-TEZ-IVA) be reimbursed for the treatment of cystic fibrosis (CF) in patients aged 6 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

For patients aged 12 years and older, 4 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 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 scores compared with remaining on the other *CFTR* modulators.

For patients aged 6 to 11 years of age, a 24-week, double-blind, placebo-controlled RCT (Study 116; N = 121) and a pivotal, single-arm, open-label trial (Study 106B; N = 66) demonstrated that treatment with ELX-TEZ-IVA resulted in clinically meaningful improvements in lung function (increase in $ppFEV_1$), nutritional status (increase in BMI z score), and health-related quality of life (increase in CFQ-R respiratory domain scores). In addition, adverse event (AE) data suggested that ELX-TEZ-IVA reduced the occurrence of pulmonary exacerbations in pediatric patients. 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.

CDEC noted that patients and clinicians stressed the importance of starting treatment with ELX-TEZ-IVA early in the disease state to prevent the irreversible damage caused by CF. Patients with $ppFEV_1$ greater than 90% were considered an important subgroup for the current review of ELX-TEZ-IVA. Input from clinical specialists, subgroup analyses from Study 116, and data from 3 observational studies suggested that ELX-TEZ-IVA may result in clinically significant improvements for patients with $ppFEV_1$ greater than 90%. Overall, CDEC concluded that there is sufficient evidence to recommend reimbursement of ELX-TEZ-IVA for patients with $ppFEV_1$ greater than 90%.

Based on the sponsor-submitted price for ELX-TEZ-IVA and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ELX-TEZ-IVA compared with best supportive care (BSC) in patients aged 6 to 11 years was $1,434,435 per quality-adjusted life-year (QALY) in the F/F genotype, $1,653,605 per QALY in the F/MF genotype, $2,437,481 per QALY in the F/RF genotype, and $1,531,443 in the F/G genotype. For the F/F genotype, ELX-TEZ-IVA was associated with an ICER of $680,560 per QALY in comparison with lumacaftor plus IVA (LUM-IVA). For the F/G genotype, ELX-TEZ-IVA was associated with an ICER of $622,381 per QALY in comparison with IVA monotherapy. In a scenario analysis assessing the cost-effectiveness of ELX-TEZ-IVA in patients 6 years and older, ICERs ranged from $1,129,990 to $1,868,095 per QALY compared with BSC. At these ICERs, ELX-TEZ-IVA is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 6 years and older with CF who have at least 1 F508del mutation in the *CFTR* gene. A reduction in price 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	Implementation guidance
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 5 RCTs and 1 single-arm pivotal study in patients with F/F, F/MF, F/G, and F/RF genotypes.	—
2. Aged 6 years and older	The indication approved by Health Canada for ELX-TEZ-IVA is limited to patients who are at least 6 years of age.	—
3. The following measurements must be completed before initiating treatment with ELX-TEZ-IVA: • baseline spirometry measurements of FEV_1 in litres and percent predicted (within the last 30 days) • 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 • number of CF-related hospitalizations in the previous 6 months • weight, height, and BMI • CFQ-R respiratory domain score.	To establish baseline values to be used for renewal of reimbursement for treatment with ELX-TEZ-IVA.	1. Weight, height, and BMI for pediatric patients are collected and reported as z scores or percentiles in clinical practice in Canada. 2. The CFQ-R instrument comprises age-appropriate versions for children aged 6 to 13 years (CFQ-C), their parents (who serve as a proxy for their child; CFQ-P), and individuals who are 14 years of age (CFQ-R teen/adult).

Reimbursement condition	Reason	Implementation guidance
4. 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.	—
5. The maximum duration of initial reimbursement is for 6 months.	The treatment effects of ELX-TEZ-IVA were generally evaluated at 24-weeks (approximately 6 months) in the studies.	—
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 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-TEZ-IVA treatment 7.4. no decline in BMI (BMI z score in children) 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 or BMI z score), 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.	Clinically significant improvements from baseline in lung function (ppFEV$_1$) and health-related quality of life (measured with the CFQ-R) are typically reported as at least 5% and 4 points, respectively. 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).

Reimbursement condition	Reason	Implementation guidance
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 previously 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 a lung transplant.	—
Prescribing		
10. Prescribing of ELX-TEZ-IVA and monitoring of treatment response should be limited to CF specialists.	Care for patients with CF 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 of Symdeko (TEZ-IVA) and Kalydeco (IVA). • IVA is also a component of Orkambi (LUM-IVA).	—
Pricing		
12. A reduction in price.	The ICER for ELX-TEZ-IVA in comparison with BSC ranged from $1,434,435 to $2,437,481 per QALY, depending on the genotype, in patients aged 6 to 11 years of age, and from $1,129,990 to $1,868,095 per QALY in patients 6 years and older. 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.	—
Feasibility of adoption		
13. The feasibility of adoption of ELX-TEZ-IVA must be addressed	At the submitted price, the budget impact of ELX-TEZ-IVA is expected to be greater than $40 million in all 3 years.	—

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.

Discussion Points

- The previous CADTH recommendation did not include sweat chloride testing as 1 of the initiation or renewal conditions for ELX-TEZ-IVA. CDEC considered the sponsor's request to include a reduction in sweat chloride as a reimbursement condition for ELX-TEZ-IVA. CDEC noted that there was consensus across the clinical experts that sweat chloride testing should not be used to evaluate the response to ELX-TEZ-IVA for the purposes of drug reimbursement because it is not clearly predictive of clinically important outcomes and only reflects the mechanism of action of *CFTR* modulators such as ELX-TEZ-IVA. The experts noted that poor adherence with the treatment over a short period of time could substantially influence the test results and that sweat chloride testing is not routinely available for use outside of establishing an initial CF diagnosis.
- CDEC noted that implementation of the CFQ-R instrument in pediatric clinical practice could require additional resources for the CF clinics to administer the CFQ-R instrument, document the responses, and track changes in scores over time. CDEC acknowledged these concerns and decided to include this as a potential criterion for consideration by the public drug programs, noting that some jurisdictions did not adopt this criterion from the previous CADTH recommendation for ELX-TEZ-IVA. Because ELX-TEZ-IVA has been shown to improve CFQ-R scores in children, adolescents, and adults, CDEC concluded that this instrument may provide a useful tool for evaluating the response to ELX-TEZ-IVA.
- CF is a rare and serious disease that is life-limiting. The F508del mutation in the *CFTR* gene is the most commonly observed mutation and, in some cases, 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 and, 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 have psychological challenges, such as depression, anxiety, and hopelessness. Patient input highlighted the following expectations for new treatment of 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), 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 very important unmet needs identified by patients.
- 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%).
- Except for IVA, the comparators used in active-controlled studies and indirect comparisons are not currently reimbursed (TEZ-IVA) or sparsely reimbursed (LUM-IVA) by the CADTH-participating drug programs.
- CDEC noted that the included studies enrolled patients who were at least 6 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 6 years of age are currently ongoing.

- CDEC discussed 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 again 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. Four of the clinical trials were 24 weeks long (Study 102, Study 106B, Study 109, and Study 116), 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 comparisons 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 on the results.

Background

Trikafta consists of a fixed-dose combination tablet containing ELX, TEZ, and IVA co-packaged with a tablet containing IVA (ELX-TEZ-IVA). ELX-TEZ-IVA is available in 2 dosage strengths:

- ELX 50 mg, TEZ 25 mg, and IVA 37.5 mg co-packaged with a tablet containing IVA 75 mg
- 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 6 years and older who have at least 1 F508del mutation in the *CFTR* gene. A deletion of phenylalanine 508 in the first nucleotide binding domain (F508del) is the most common mutation in the *CFTR* gene that results in CF. The Canadian Cystic Fibrosis Registry reported that there were 4,344 people in Canada living with CF in 2019. Of these, 87.8% of patients carried at least 1 F508del mutation (47.1% were homozygous and 40.7% were heterozygous).

Submission History

This is the second submission to CADTH for ELX-TEZ-IVA. CADTH has previously reviewed ELX-TEZ-IVA for the treatment of CF in patients aged 12 years and older who have at least 1 F508del mutation in the *CFTR* gene; CDEC recommended that ELX-TEZ-IVA be reimbursed with conditions.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 4 of RCTs in adolescents and adults (Study 102, Study 103, Study 104, and Study 109), 1 RCT and 1 single-arm pivotal trial in children (Study 116 and Study 106B); 2 long-term extension phase studies (Study 105 and Study 107), indirect comparisons 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 3 observational descriptive analyses in patients with $ppFEV_1$ greater than 90% in a real-world setting
- patient perspectives gathered by 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, including input from panels of clinical specialists with expertise diagnosing and treating patients living with CF (5 clinicians in the previous review and 4 clinicians in the current review)
- input from 3 clinician groups on the previous review of ELX-TEZ-IVA for adolescents and adults (the Canadian Cystic Fibrosis Clinic Directors, Cystic Fibrosis Canada's Accelerating Clinical Trials Network, and the Toronto Adult CF Clinic) and 2 clinician groups for the current review of ELX-TEZ-IVA (CF Canada's Accelerating Clinical Trials Network and the Canadian Cystic Fibrosis Clinic Directors/CF Canada Healthcare Advisory Council)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Three patient groups, CF Canada, the Canadian Cystic Fibrosis Treatment Society, and CF Get Loud, responded to CADTH's call for patient input for both the initial CADTH review of ELX-TEZ-IVA (i.e., for patients 12 years and older) and for the subsequent review of ELX-TEZ-IVA, which focused on patients 6 years and older.

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 have 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 have CF-related comorbidities, such as CF-related diabetes and CF-related liver disease. In addition to the decline in the physical health of patients with CF, many patients also have 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 often cannot be quantified. 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. CF has a significant impact on an individual's day-to-day quality of life and affects their life decisions, including 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, improved digestive health, better energy levels, and minimizing symptoms of CF. Patients want to avoid hospital admissions and reduce the need for invasive medical procedures and 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.

Patient groups emphasized the importance of early and aggressive treatment of CF with a focus on maintaining health and slowing or preventing disease progression. They noted that even those children with CF who appear healthy (e.g., $ppFEV_1$ of 100%) are subjected to an aggressive therapeutic regimen of physiotherapy and antibiotic treatments in addition to special diets and frequent clinic visits. All patient groups stressed that it is important to start treatment with ELX-TEZ-IVA as soon as possible to prevent the irreversible damage caused by CF. The patient groups referenced the initial CADTH recommendation for ELX-TEZ-IVA noting that they believe the reimbursement conditions are too restrictive, particularly the requirement that patients demonstrate $ppFEV_1$ less than 90% to be eligible. The patient groups believe that all patients with at least 1 F508del mutation can benefit from treatment with ELX-TEZ-IVA.

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 people 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 in 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 will be most likely to respond to ELX-TEZ-IVA. The patients who are most in need of treatment with ELX-TEZ-IVA include patients with moderate to severe lung disease (e.g., $ppFEV_1 \leq 60\%$), patients whose BMI is less than or equal to 20 kg/m^2, patients with frequent pulmonary exacerbations, and those experiencing a rapid decline in FEV_1. However, all patients, including those with mild lung disease or who are pre-symptomatic, could potentially benefit from treatment with ELX-TEZ-IVA considering the long-term outcomes and the 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 that are significantly less effective (e.g., LUM-IVA [Orkambi] and TEZ-IVA plus IVA [Symdeko]) and patients currently receiving those drugs would likely be switched to ELX-TEZ-IVA.

The following end points are routinely assessed in Canadian clinical practice: lung function (e.g., spirometry measures such as FEV_1), nutrition and growth (e.g., BMI, BMI z score, and BMI percentile), 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). For $ppFEV_1$, an improvement in $ppFEV_1$ of greater than or equal to 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 most likely be interrupted or discontinued because of AEs or progression to lung transplant. The most likely known AE that would result in discontinuation would be development of persistent liver enzyme abnormalities.

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

Clinician Group Input

Three groups of clinicians provided input for the initial CADTH review of ELX-TEZ-IVA (the Canadian Cystic Fibrosis Clinic Directors (CCFCD), CF Canada's Accelerating Clinical Trials Network, and the Toronto Adult CF Clinic) and 2 groups provided input for the current review (CF Canada's Accelerating Clinical Trials Network and the Canadian Cystic Fibrosis Clinic Directors/CF Canada Healthcare Advisory Council). The input from the clinician groups identified the same unmet medical needs for patients with CF 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 process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for ELX-TEZ-IVA:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy.

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Implementation issues from the review of ELX-TEZ-IVA in patients 6 years and older	
Considerations for initiation of therapy	
Unlike the pivotal trials for patients aged 12 years and older, patients with ppFEV$_1$ ≥ 90% were eligible for the trials conducted in patients aged 6 to 11 years. The drug programs have noted that a discrepancy in recommended reimbursement criteria for the 2 patient populations (i.e., those aged 6 to 11 years and those 12 years and older) would be challenging for the drug programs to operationalize. Is there evidence to suggest that these patients would benefit from treatment with ELX-TEZ-IVA?	The pediatric trials enrolled patients with FEV$_1$ > 70% (and 46% of patients had ppFEV$_1$ > 90% in Study 116 and Study 106B, respectively). These trials demonstrated meaningful improvements in lung clearance index, FEV$_1$, BMI z score, and CFQ-R. Therefore, ELX-TEZ-IVA has been shown to have clinical benefit for pediatric patients with ppFEV$_1$ > 90%. For those patients aged 12 years and older, the PROMISE study suggested that patients with ppFEV$_1$ > 90% at the time of initiating treatment with ELX-TEZ-IVA experienced improvements in ppFEV$_1$ (absolute change of 6.52%; 95% CI, 5.18% to 7.86%); BMI (absolute change of 0.82 kg/m^2; 95% CI, 0.50 to 1.13); and CFQ-R (absolute change of 15.66; 95% CI, 12.80 to 18.52).
Considerations for continuation or renewal of therapy	
Can the clinical experts confirm that multiple breath washout tests are only available at specialty clinics at children's hospitals and not available at all pulmonary function testing clinics?	This measurement is not currently used in routine Canadian clinical practice.

Drug program implementation questions	Clinical expert response
Prior implementation issues from the review of ELX-TEZ-IVA in patients aged 12 years and older	
Considerations for initiation of therapy	
Patients with ppFEV$_1$ greater than 90% at screening were excluded from the pivotal and supportive phase III trials. Is there evidence to suggest that these patients would benefit from treatment with ELX-TEZ-IVA?	The clinical experts noted that these patients may benefit from treatment with ELX-TEZ-IVA. However, prioritization should be for those patients with more significant disease burden.
Patients with ppFEV$_1$ less than 40% at screening were excluded from the pivotal and supportive phase III trials. Is there evidence to suggest that these patients would benefit from treatment with ELX-TEZ-IVA?	Subgroup data from Study 102 and 2 observational studies included in the CADTH review provided short-term data on the efficacy and safety of ELX-TEZ-IVA in patients with CF and who had advanced pulmonary disease. These studies suggested that treatment with ELX-TEZ-IVA resulted in a clinically meaningful improvement in ppFEV$_1$ for patients who had a baseline ppFEV$_1$ less than 40%. The clinical experts consulted by CADTH, the clinician groups who provided input, and the patient groups who provided input have all noted anecdotal evidence, based on clinical experience, that ELX-TEZ-IVA is beneficial for those with advanced lung disease.
The product monograph indicates that patients with severe hepatic impairment should not be treated with ELX-TEZ-IVA. Would these recommendations be followed in clinical practice?	The clinical experts consulted by CADTH suggested that clinicians may attempt to treat those with severe hepatic impairment using ELX-TEZ-IVA at a reduced dosage, as opposed to using the reduced dosages of the alternative *CFTR* modulators, which are unlikely to provide the same level of clinical benefit. It was noted that therapeutic trials should be considered for all patients when the potential for benefit exceeds the risk.
Considerations for continuation or renewal of therapy	
What clinical outcome measures should be used to assess therapeutic response to treatment with ELX-TEZ-IVA?	The following end points have been suggested for adult patients: • improvement in or stabilization of a declining FEV$_1$ • improvement in exacerbation frequency • improvement in BMI.
What magnitude of improvement would be clinically significant for ppFEV$_1$? What would be the appropriate intervals for evaluating response to treatment?	For typical patients in Canadian practice, an improvement in ppFEV$_1$ of greater than or equal to 5% would typically be considered clinically meaningful. However, the magnitude of improvement in ppFEV$_1$ that would be considered clinically significant depends on the baseline status of the patient. Those with a very low ppFEV$_1$ may see smaller improvements from baseline, but even stabilization in such patients can be clinically important. FEV$_1$ is routinely assessed in the target population and the experts noted that evaluations could be performed 3 to 4 times per year.
What magnitude of improvement would be clinically significant for BMI? What would be the appropriate intervals for evaluating response to treatment based on BMI?	The experts noted that increases in BMI should only be viewed as a marker of improvement in patients who are malnourished. (i.e., BMI < 20). For those patients, the goal of therapy is to increase BMI into the normal range.
Should therapeutic response be assessed using different criteria for patients who are naive to *CFTR* modulator therapy	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*

Drug program implementation questions	Clinical expert response
compared with those who are switching from a different *CFTR* modulator to ELX-TEZ-IVA?	modulators that are significantly less effective (e.g., Orkambi and Symdeko) and patients currently receiving those drugs would likely be switched to ELX-TEZ-IVA.
What clinical criteria could be used to identify patients with rapidly progressive disease?	The clinical experts noted that there are no currently accepted definitions for patients with rapidly progressive disease.
What clinical criteria could be used to determine if patients are non-responders to treatment with ELX-TEZ-IVA (i.e., potential discontinuation criteria)?	Based on the available evidence, non-responders to ELX-TEZ-IVA are likely to be rare. The primary reasons for discontinuing treatment are likely to be related to adverse events (e.g., abnormal liver function test results, rash, or excessive weight gain).
Considerations for prescribing of therapy	
Should prescribing be limited to physicians with expertise in the management of CF?	The only setting appropriate for assessment of patients for appropriateness for this treatment, initiation of treatment, and monitoring of treatment is in an adult or pediatric CF clinics.

BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ELX = elexacaftor; FEV_1 = forced expiratory volume in 1 second; IVA = ivacaftor; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second TEZ = tezacaftor.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Patients Aged 6 to 11 Years

Description of Studies

The evidence identified in the current review of ELX-TEZ-IVA that addressed the expanded patient population (i.e., those between the ages of 6 and 11 years) included a 24-week, double-blind, placebo-controlled RCT in patients who were heterozygous for the F508del mutation and had 1 minimal function mutation (F/MF) (Study 116; N = 121) and a 24-week, pivotal, single-arm trial in patients who were homozygous for the F508del mutation (F/F) and F/MF (Study 106B; N = 66). The treatment periods were 24 weeks in Study 116 and Study 106B, and both 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). Study 106B is the second phase of a 2-part study (Part A consisted of a 28-day screening period; a 15-day, single-arm, open-label treatment period; and a 28-day safety follow-up period). Part B was initiated after completion of the internal review of the data in Part A that was used to confirm or adjust the doses to be evaluated in Part B. In accordance with recommended dosage for ELX-TEZ-IVA in Canada, this report has focused on Part B (i.e., Study 106B).

The inclusion and exclusion criteria for the included RCTs were similar except for the *CFTR* genotypes (i.e., only F/MF in Study 116 and F/F or F/MF in Study 106B) and the thresholds for $ppFEV_1$ (≥ 70% in Study 116 and ≥ 40% in Study 106B) and lung clearance index 2.5 (LCI2.5) (≥ 7.5 in Study 116 and not specified for Study 106). Similar to the trials conducted in adult and adolescent patients, patients in Study 116 and Study 106B were required to have stable CF disease in the opinion of the investigator 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 first dose of 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), abnormal liver function, or abnormal renal function.

The primary end point of Study 116 was absolute change from baseline in LCI2.5; secondary end points were absolute change from baseline in sweat chloride, CFQ-R respiratory domain score, and CFQ-R non-respiratory domain scores. All efficacy end points in Study 106B were considered secondary objectives; the primary end point was safety and tolerability. The end points included absolute changes from baseline in the following: $ppFEV_1$, LCI2.5, CFQ-R, BMI, BMI z score, weight, weight z score, height, and height z score. In addition, descriptive statistics were provided for pulmonary exacerbations and hospitalization in Study 106B.

Efficacy Results

In Study 116, treatment with ELX-TEZ-IVA was associated with an increase from baseline in $ppFEV_1$ compared with placebo through 24 weeks with a least squares mean difference (LSMD) of 11.0% (95% CI, 6.9% to 15.1%). 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. In Study 106B, treatment with ELX-TEZ-IVA resulted in a within-group increase in $ppFEV_1$ through 24 weeks (LS mean change = 10.2%; 95% CI, 7.9% 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 greater than baseline at all time points throughout the 24-week treatment period. The sponsor provided post hoc subgroup analyses for those with $ppFEV_1$ of 90% or less at baseline, and the increase from baseline in $ppFEV_1$ was [redacted] for those with $ppFEV_1$ of 90% or less at baseline and [redacted] for those with $ppFEV_1$ greater than 90% at baseline.

In Study 116, treatment with ELX-TEZ-IVA was associated with a reduction in LCI2.5 through 24 weeks compared with placebo (LSMD = −2.26; 95% CI, −2.71 to −1.81; P < 0.0001). Patients in Study 106 demonstrated a within-group reduction in LCI2.5 through 24 weeks (LS mean change = −1.71; 95% CI, −2.11 to −1.30; P < 0.0001). Improvements (reduction) in LCI2.5 with ELX-TEZ-IVA were observed at the time of the first post-baseline assessment (i.e., day 15) and were reduced at all time points throughout both studies.

Pulmonary exacerbations were only captured as AEs in Study 116. The percentage of patients with at least 1 pulmonary exacerbation was greater in the placebo group compared with the ELX-TEZ-IVA group (26.2% versus 1.7%). Pulmonary exacerbations were included as an exploratory end point in Study 106B. In Study 106B, the annual event rate for overall pulmonary exacerbations was 0.12 events per year. Event rates for pulmonary exacerbations requiring hospitalization and/or IV antibiotic therapy were each 0.03 events per year. There were no statistical comparisons for event rates pre- and post-treatment with ELX-TEZ-IVA.

In Study 116, treatment with ELX-TEZ-IVA was associated with improved health-related quality of life as measured with the CFQ-R respiratory domain score from baseline compared with placebo through 24 weeks (LSMD = 5.5; 95% CI, 1.0 to 10.0; P = 0.0003). In Study 106B, patients demonstrated an increase from baseline CFQ-R respiratory domain scores through 24 weeks (LS mean absolute change = 7.0; 95% CI, 4.7 to 9.2; P < 0.0001). Changes from baseline in the non-respiratory domains of the CFQ-R were assessed as exploratory end points in Study 106B (but not in Study 116). Scores in non-respiratory domains of the CFQ-R showed a numerical increase from baseline; however, no statistical analyses were conducted.

Absolute change from baseline in sweat chloride through 24 weeks was a secondary end point of Study 116. The ELX-TEZ-IVA group demonstrated statistically significant reductions in sweat chloride compared with the placebo group through 24 weeks (LSMD: = −51.2 mmol/L; 95% CI, −55.3 to −47.1). In Study 106B, treatment with ELX-TEZ-IVA resulted in a statistically significant within-group reduction in sweat chloride through 24 weeks. The LS mean absolute change in sweat chloride from baseline through 24 weeks was −60.9 mmol/L (95% CI, −63.7 to −58.2; P < 0.0001).

Harms Results

In Study 116, the overall percentage of patients who experienced at least 1 AE was greater in the placebo group (93.4%) compared with the ELX-TEZ-IVA group (80.0%). AEs that were reported in at least 5% of patients in the ELX-TEZ-IVA group and occurred at 5% or higher frequency compared with the placebo group were headache (30.0% versus 19.7%), rash (10.0% versus 4.9%), and positive *Staphylococcus* test (6.7% versus 1.6%). Infective pulmonary exacerbations were more commonly reported as AEs in the placebo group compared with the ELX-TEZ-IVA group (26.2% versus 1.7%). AEs were more commonly reported in Study 106B compared with the ELX-TEZ-IVA group of Study 116 (e.g., at least 1 AE was reported in 98.5% of patients in Study 106B compared with 80.0% in Study 116). In Study 116, 4 patients (6.7%) in the ELX-TEZ-IVA group and 9 (14.8%) patients in the placebo group had at least 1 serious AE (SAE). In Study 106B, 1 patient (1.5%) had 3 SAEs (metapneumovirus infection, pneumonia, and rhinovirus infection). In Study 116, 1 patient (1.7%) in the ELX-TEZ-IVA group had an AE of rash that led to study drug discontinuation. No patients in the placebo group discontinued the study drug. In Study 106B 1 patient had an AE of rash erythematous that led to treatment discontinuation.

Critical Appraisal

Randomization in Study 116 was performed using an appropriate methodology with adequate allocation concealment (i.e., interactive web response system) and stratification based on relevant prognostic factors (i.e., baseline lung function [LCI2.5 < 10 versus ≥ 10] and baseline weight [< 30 kg versus ≥ 30 kg]). Baseline and demographic characteristics were generally similar across the ELX-TEZ-IVA and placebo groups in Study 116. A higher percentage of patients in the ELX-TEZ-IVA group had a baseline $ppFEV_1$ greater than 90% [redacted] and lower percentage had a baseline $ppFEV_1$ less than 70% [redacted]. Because those with normal lung function (i.e., > 90%) would be less likely to demonstrate short-term improvements in $ppFEV_1$ due to a ceiling effect, this could potentially bias the results for change in $ppFEV_1$ through 24 weeks against ELX-TEZ-IVA.

The study treatments were administered in a double-blind manner in Study 116 and open-label manner in Study 106. The AE profiles of ELX-TEZ-IVA and the comparators were unlikely to compromise blinding in the study. The exception could be the increased percentage of patients who experienced a rash in the ELX-TEZ-IVA group (13.3% versus 4.9% with placebo); however, it is not expected that this would have seriously impacted treatment blinding. Similar to the previously reviewed trials in adults and adolescents, there were few pediatric patients who discontinued either Study 116 (99.2% completion) or Study 106B (97.0% completion). The studies were relatively short in duration, which may explain in part the high percentage of patients who completed. Adherence was reported to be 99% across both Study 116 and Study 106B. In accordance with the study protocols, the use of concomitant medications remained stable throughout the treatment period for all treatment groups. Pulmonary exacerbations pediatrics were only evaluated as efficacy end points in the 24-week single-arm study (Study 106B). The placebo-controlled trial (Study 116) only reported pulmonary exacerbations as

AEs. The primary and key secondary end points were analyzed without statistical testing procedures to control the potential for type I error; therefore, the results should be interpreted with caution due to the risk of inflated type I error.

The diagnostic criteria used to screen patients for Study 116 and Study 106 were identical to those used in Study 102, Study 103, and Study 109 for patients at least 12 years of age. As noted in the previous CADTH review of ELX-TEZ-IVA, these criteria are consistent with Canadian clinical practice for diagnosing patients with CF who are homozygous for the F508del-*CFTR* mutation. The clinical experts consulted by CADTH indicated that the exclusion of patients with $ppFEV_1$ less than 70% does not impact the generalizability of Study 116 because these patients are less common in the Canadian pediatric CF population.

Study 106B included outcomes that are considered to be important to patients with CF based on patient group input: respiratory function (i.e., LCI and $ppFEV_1$), nutritional status and growth (e.g., weight, height, and BMI), health-related quality of life (CFQ-R), and clinical events (e.g., pulmonary exacerbations). The primary efficacy end point in Study 116 (i.e., LCI2.5) differed from that used in the adolescent/adult trials (i.e., $ppFEV_1$). This is reflective of regulatory guidance, which notes that spirometry may not be sensitive enough to detect treatment differences in children with CF. Younger patients with CF may demonstrate spirometry values that are within the normal range, but there may be underlying structural deficiencies within the lungs that can be detected using alternative evaluations (e.g., LCI).

The use of placebo as the comparator in Study 116 is appropriate because no other *CFTR* modulators are currently approved in Canada to treat patients with CF aged 6 to 11 years with an F/MF genotype. The absence of a control group in Study 106B limits the ability to interpret the results of the study. In both studies, ELX-TEZ-IVA (or matching placebo in Study 116) was added to the existing therapeutic regimens used by the patients, which is reflective of how ELX-TEZ-IVA would be administered in clinical practice. The clinical experts consulted by CADTH indicated that the background therapies used in Study 116 and Study 106B were reasonably reflective of the CF population in Canada.

Patients Aged 12 Years and Older

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 in which all patients with either an F/F or F/RF genotype received treatment with TEZ-IVA + 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 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 first dose of 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), liver function, or 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 (LSMD = 13.8%; 95% 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 [redacted] 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). Based on hazard ratios (HRs), treatment with ELX-TEZ-IVA compared with placebo was associated with longer 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 increase 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 increase in BMI z score 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 CCFQ-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 mmol/L; 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 and 17 years. At 24 weeks, the ELX-TEZ-IVA group demonstrated improvements compared with placebo group in scores for the domains of 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 AEs in Study 103 and Study 109. The percentage of patients with at least 1 pulmonary exacerbation was greater in the TEZ-IVA compared with the ELX-TEZ-IVA group in both studies.

Compared with treatment 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 treatment 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 (LSMD = −45.1 mmol/L; 95% CI, −50.1 to −40.1) in Study 103 and through 24 weeks in Study 109 (LSMD = −42.8 mmol/L; 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 and 17 years. The ELX-TEZ-IVA group demonstrated improvements compared with the TEZ-IVA group in scores for the domains of 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 (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 with 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 treatment 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 AEs. Compared with the pooled control group (TEZ-IVA and IVA), fewer patients 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). The ELX-TEZ-IVA group also showed 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). In subgroup analyses, similar effect sizes were seen for treatment with ELX-TEZ-IVA compared with treatment with IVA in patients with an F/G genotype (LSMD = 8.9; 95% CI, 3.8 to 14.0; P = 0.0008) and for treatment with ELX-TEZ-IVA compared with treatment 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). The ELX-TEZ-IVA group also showed a decrease in sweat chloride from baseline compared with 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 AE was 96.0% in the placebo group and 93.1% in the ELX-TEZ-IVA group. The percentage of patients who experienced at least 1 SAE was 20.9% in the placebo group and 13.9% in the ELX-TEZ-IVA group. Pulmonary exacerbations were the most reported SAE and were more frequent in the placebo group compared with the ELX-TEZ-IVA group (16.4% versus 5.4%). There were few other SAEs that were reported for more than 1 patient in each treatment group. There were 2 withdrawals due to AEs (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 AE in the TEZ-IVA group was 63.5% and 88.5% in Study 103 and Study 109, respectively compared with 58.2% and 92.0% in the ELX-TEZ-IVA group, respectively. 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 in Study 109. 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, and only reported for 1 patient in the TEZ-IVA group (pulmonary exacerbation) and 2 patients in the ELX-TEZ-IVA group (pulmonary exacerbation and rash) (1.9% versus 3.6%). 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 AE 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 ELXTEZ-IVA group (5.6% versus 1.5%). There were 2 WDAEs from the control group (1.6%; pulmonary exacerbation, 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 usage [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 AE 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%), although the studies were relatively short in duration which may in part explain the high percentage of patients who completed. Adherence with the study treatments was reported to be more 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 a 4-week open-label, active-treatment period with TEZ-IVA or IVA before randomization. As such, these trials were essentially 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 to CADTH to provide an estimate of ELX-TEZ-IVA versus placebo for those with an F/F or F/RF genotype.

Indirect Comparisons

Patients Aged 6 to 11 Years

Description of Studies

The sponsor conducted a single indirect treatment comparison (ITC) for patients aged 6 to 11 years with an F/F genotype to derive relative estimates of clinical efficacy for ELX-TEZ-IVA versus LUM-IVA, ELX-TEZ-IVA versus placebo, and ELX-TEZ-IVA versus TEZ-IVA. TEZ-IVA is not currently approved by Health Canada or reimbursed by the Canadian public drug programs for use in patients aged 6 to 11 years. To conduct the primary indirect comparisons, the sponsor extracted 24-week individual patient data for those with an F/F genotype from the following studies: [redacted]. Additional sensitivity analyses were performed using 8-week data.

Efficacy Results

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 LCI2.5, [redacted] for BMI z score, and [redacted] for the CFQ-R respiratory domain. The sponsor reported the following indirect estimates of effect for ELX-TEZ-IVA compared with LUM-IVA for absolute change from baseline through 24 weeks: [redacted] for ppFEV$_1$, [redacted] for LCI2.5, [redacted] for BMI z score, and [redacted] for the CFQ-R respiratory domain.

Harms Results

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

Critical Appraisal

The primary limitation of the ITC was the difference in study design across the included studies [redacted].

Patients Aged 12 Years and Older

Description of Studies

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 because of the lack of RCTs. 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 patients 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 CADTH's 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 the studies for TEZ-IVA, LUM-IVA, and IVA all 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 and 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 AEs.

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 the 4-week open-label, 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

CADTH also reviewed additional studies that did not meet the eligibility criteria of the systematic review but may address important gaps in the evidence from the pivotal and

supportive RCTs. These included 2 long-term extension phase studies (Study 107 and Study 105), 2 indirect comparisons 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 3 observational studies that included a subset of patients with normal lung function at the time of initiating treatment with ELX-TEZ-IVA.

Long-Term Extension Studies

Patients Aged 6 to 11 Years

Study 107 is an ongoing, multi-centre, open-label extension (OLE) study that enrolled patients who completed Study 106 (i.e., children with CF aged 6 years and older who are either an F/F genotype or F/MF genotype). Two participants discontinued the study drug before week 24 of Study 106 and did not enter Study 107. Interim results were reported after all patients (N = 64) had completed the 24-week visit.

Efficacy Results

Treatment resulted in improvements in all measures consistent with Study 106. Compared to baseline values of Study 106, ELX-TEZ-IVA treatment improved ppFEV$_1$ (9.5%; SE = 1.3%), sweat chloride concentration (−64.7 mmol/L; SE = 1.7), CFQ-R respiratory domain score (12.9 points; SE = 1.2), BMI (1.27 kg/m^2; SE = 0.15), BMI z score (0.34; SE = 0.06), and LCI2.5 (−1.91; SE = 0.18) at the extension study week 24 interim analysis. Overall, in the 24-week pivotal study and through week 24 interim analysis of the OLE study, 5 children (7.6%) had protocol-defined pulmonary exacerbations, with an observed annual rate of pulmonary exacerbations of 0.07. There were no CF-related hospitalizations in either the pivotal study or through week 24 interim analysis of the OLE study.

Harms Results

Most patients (79.7%) reported AEs that were either mild (51.6%) or moderate (28.1%) in severity. The most common AEs were upper respiratory tract infection (14.1%), headache (10.9%), and vomiting (10.9%). There were no discontinuations through the week 24 interim analysis.

Critical Appraisal

Study 107 is an extension of Study 106, which was critically appraised previously. The findings from this interim analysis were retrieved from a poster presentation at the North American Cystic Fibrosis Conference, and no further details were provided by the sponsor; therefore, CADTH could not fully critically appraise this study at the time of this review. Two patients discontinued the study drug before week 24 and did not enter the OLE study but there is no explanation for this. Issues with the generalizability of these data are the same as for the parent double-blind study.

Patients Aged 12 Years and Older

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). Results from the week 96 interim analysis were presented at the North American Cystic Fibrosis Conference. A total of 506 patients were enrolled in the extension study (n = 400 from Study 102 and n = 107 from Study 102) and 42 participants prematurely discontinued treatment before the week 96 visit; reasons

included AEs (n = 8), pregnancy (n = 6), refused further dosing (n = 9), commercial drug availability (n = 12), and other reasons (n = 7).

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 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 patients switched from TEZ-IVA to ELX-TEZ-IVA and 14.3 (95% CI, 9.5 to 19.2) for patients who were 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 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.

Among patients previously enrolled in Study 102, the absolute change from week 24 to week 96 in $ppFEV_1$ was similar for patients who switched from placebo to ELX-TEZ-IVA (absolute change = 15.2%; 95% CI, 13.6 to 16.7) and for those who remained on ELX-TEZ-IVA (absolute change = 14.3%; 95% CI, 12.7 to 15.8) during the extension study. Patients previously enrolled in Study 103 reported an absolute change from week 4 to week 96 in $ppFEV_1$ of 12.4% (95% CI, 9.6% to 15.1%) and 11.5% (95% CI, 8.8% to 14.2%) during the extension study for patients previously treated with TEZ-IVA and ELX-TEZ-IVA, respectively.

The estimated mean pulmonary exacerbation rate per 48 weeks for participants with F/MF genotypes was 0.21 (95% CI, 0.17 to 0.26) for the 96-week interim analysis compared with 0.98 in the placebo group of the F/MF parent study. The estimated mean pulmonary exacerbation rate per 48 weeks for participants with the F/F genotype was 0.21 (95% CI, 0.14 to 0.30) for the 96-week interim analysis. Because part of this OLE study overlapped with the COVID-19 pandemic, restrictions on social interactions likely contributed to reductions in pulmonary exacerbation for patients with CF.

For patients previously enrolled in Study 102, the absolute change from week 24 to extension period week 96 in the CFQ-R respiratory domain was 20.1 points (95% CI, 17.5 to 22.6) for those switched from placebo to ELX-TEZ-IVA, and 21.7 points (95% CI, 19.1 to 24.1) for those who received ongoing ELX-TEZ-IVA treatment. The absolute change was 15.6 points (95% CI, 11.0 to 20.1) and 18.0 points (95% CI, 13.6 to 22.5) for patients from Study 103, respectively,

who were switched from TEZ-IVA to ELX-TEZ-IVA, and those treated with ELX-TEZ-IVA in both study periods. The absolute change in BMI from week 24 (Study 102) or week 4 (Study 103) to week 96 ranged from 1.3 kg/m^2 to 1.9 kg/m^2. The absolute change in sweat chloride concentration from week 24 (study 102) or week 4 (study 103) to week 96 ranged from −45.8 mmol/L to −49.7 mmol/L in patients previously enrolled in Study 102 or 103.

Harms Results

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

Most patients (98%) reported at least 1 AE during the extension study (586 events per 100 person years). The most reported events were infective pulmonary exacerbation of CF (38%), cough (36%), oropharyngeal pain (26%), headache (25%), and nasopharyngitis (23%). Eleven patients (2.2%) stopped treatment due to AEs, 126 patients (25%) experienced an SAE, and grade 3 or 4 AEs were reported by 84 patients (17%).

Critical Appraisal

Study 105 is an ongoing, uncontrolled, open-label trial that enrolled patients who had completed Study 102 or Study 103. As this was an unblinded study, patient's expectations of treatment could potentially have 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 7 patients (1.4%) of the 513 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 (9 patients, 1.8%); 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. The findings from the week 96 OLE interim analysis were retrieved from a poster presentation at the North American Cystic Fibrosis Conference, and no further details were provided by the sponsor.

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 (Adults)

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. The mean age of patients was 34.4 years (range = 19 to 46 years). 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 (SD = 0.17) events per month in the 12 months before receiving treatment with ELX-TEZ-IVA, and 0.04 (SD = 0.07) events per month during the 4.9-month follow-up period (P < 0.001).

French Cohort (Adolescents and Adults)

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 median age of the treated patients was 31 years (interquartile range, 24 to 38), of which 17 (7%) were adolescents. The mean change from baseline in 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 1- and 3-month assessments. 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. Before initiation of ELX-TEZ-IVA treatment, 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 had died while waiting for transplant (0.4%).

Critical Appraisal

The 2 observational studies provided descriptive data on the effects of ELX-TEZ-IVA in patients with CF who had 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 results should be interpreted with caution because of 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.

Observational Studies in Patients With Normal Lung Function

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. At the time of the interim analysis, there were data available from [redacted] with ppFEV$_1$ greater than 90% at the time of enrolment. The sponsor reported that this subgroup of patients had a mean baseline ppFEV$_1$ of [redacted] before starting treatment and a mean ppFEV$_1$ of [redacted] after an average [redacted] months of treatment. No interim data were reported for change from baseline in BMI and BMI z score, pulmonary exacerbations, pulmonary exacerbations requiring IV antibiotics, or pulmonary exacerbations requiring hospitalization, although these were pre-specified end points in the HELIO study.

US Cystic Fibrosis Foundation Patient Registry

The sponsor provided an unpublished analysis from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Individuals who met the following criteria were included in the analysis: had a CFFPR record of initiating treatment with ELX-TEZ-IVA between October 21, 2019, and December 31, 2019; were at least 12 years of age on the date of initiating treatment with ELX-TEZ-IVA; had an F/MF or F/F genotype; had a ppFEV$_1$ assessment available both within 90 days before and any time after ELX-TEZ-IVA initiation through March 15, 2020 (cut-off

date); and the last ppFEV$_1$ measurement before ELX-TEZ-IVA initiation (baseline) was greater than 90%. There were [redacted] F/MF and [redacted] F/F patients who met the inclusion criteria. The mean age of patients in the F/MF and F/F subgroups were [redacted] and [redacted] years, respectively. Among F/F patients [redacted] patients ([redacted]) had previously been exposed to a *CFTR* modulator before initiation of ELX-TEZ-IVA. Among F/MF patients || patients ([redacted]) had previously been exposed to a *CFTR* modulator before ELX-TEZ-IVA initiation. The mean baseline ppFEV$_1$ values for patients in the F/MF and F/F subgroups were [redacted] and [redacted], respectively. The mean change in ppFEV$_1$ from baseline in the F/MF and F/F subgroup of patients with a baseline ppFEV$_1$ greater than 90% were [redacted] and [redacted], respectively. Similar to the HELIO study, no statistical analyses were reported and there were no other end points assessed.

PROMISE Study

The PROMISE study is an ongoing prospective observational study to understand the effects of ELX-TEZ-IVA in clinical use in the US. The study is sponsored by CF Foundation, and programmatic funding was provided by the National Institutes of Health. Patients were included if they met the following criteria: participants were at least 12 years of age, had at least 1 copy of F508del, and the intent to initiate ELX-TEZ-IVAIVA by the participant's physician. Due to restrictions during the COVID-19 pandemic, the time frame to complete the pre-planned 6-month assessment was extended, and results were reported. Additional 18- and 30-month study visits are planned. The average age of patients in the interim dataset meeting the inclusion and exclusion criteria (N = 487) was 25.1 years. Almost half the patients were F/F genotype (48.5%), 26.7% (n = 130) of patients had a baseline ppFEV$_1$ of less than 65%, and 40.2% (n = 196) had a baseline ppFEV$_1$ greater than or equal to 90%. For patients who completed the 6-month visit (n = 356) and for the subgroup of patients with ppFEV$_1$ greater than 90% (n = 148), the mean change in ppFEV$_1$ from baseline was 9.8 points and 6.5 points, respectively. The mean change in sweat chloride concentration from baseline for patients who completed the 6-month visit (n = 383) and for the subgroup of patients with ppFEV$_1$ greater than 90% (n = 158) was −41.7 mmol/L and −39.7 mmol/L, respectively. The mean change in CFQ-R respiratory domain scores for patients who completed the 6-month visit (n = 302) and for the subgroup of patients with ppFEV$_1$ greater than 90% (n = 120) was 20.4 points and 15.7 points, respectively. The mean change in BMI for adult patients who completed the 6-month visit (n = 326) and for the subgroup of patients with ppFEV$_1$ greater than 90% (n = 76) was 1.2 kg/m^2 and 0.8 kg/m^2, respectively. The mean change in BMI z score for pediatric patients who completed the 6-month visit (n = 139) and for the subgroup of patients with ppFEV$_1$ greater than 90% (n = 93) was 0.3 and 0.3, respectively.

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 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 patients with CF who may receive ELX-TEZ-IVA and the impact of treatment on pulmonary exacerbations.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation
Target population	Patients with CF aged 6 years and older who have at least 1 F508del mutation in the *CFTR* gene, represented by the following 4 genotypes considered in separate analyses: • F/F genotype • F/MF genotype • F/RF genotype • F/G genotype (including F/R117H).
Treatment	ELX-TEZ-IVA with background BSC
Submitted price	ELX-TEZ-IVA (Trikafta), 100 mg/50 mg/75 mg and IVA 150 mg tablets, or 50 mg/25 mg/37.5 mg and IVA 75 mg tablets: $840 per daily dose
Annual cost	At the recommended dosage of 2 tablets of ELX-TEZ-IVA taken in the morning and 1 tablet of IVA taken in the evening, the annual cost is $306,810 per patient, regardless of strength
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. • LUM-IVA in patients with an F/F genotype, in combination with BSC • IVA in patients with an F/G genotype or F/R117H genotype, in combination with BSC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (approximately 92 years)
Key data source	• Baseline patient characteristics were derived for each genotype separately from a number of trials of *CFTR* modulators in these populations. • Baseline mortality hazard was estimated based on an age-specific mortality from a CF population survival curve derived from the literature. This survival was adjusted for changes in clinical characteristics using a Cox proportional hazards model. • The sponsor commissioned an indirect treatment comparison to inform placebo-adjusted estimates for acute change in $ppFEV_1$ and mean change in weight-for-age z score in the F/F population for patients on *CFTR* modulators. Data for the F/MF population were based on Study 116, while the data for the F/RF and F/G populations were extrapolated from trial data for the population aged 12 years and older. Patients on BSC were assumed to not experience any increase in either outcome. • Impact of treatment on long-term rate of decline in $ppFEV_1$ 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.
Key limitations	• There is no evidence of the long-term effect of ELX-TEZ-IVA on the rate of decline in $ppFEV_1$ or on pulmonary exacerbations in comparison with BSC, LUM-IVA, or IVA monotherapy. This leads to substantial uncertainty with the cost-effectiveness of ELX-TEZ-IVA. • The sponsor incorporated dynamic pricing of ELX-TEZ-IVA and IVA based on an assumption of generic

Component	Description
	entry. This assumption is associated with considerable uncertainty and likely underestimates the total costs associated with ELX-TEZ-IVA and IVA. • Drug acquisition costs were adjusted for patient compliance, although treatment efficacy was not. Drug wastage may occur; however, drugs will still be dispensed and paid for by public drug plans. This underestimated the total drug costs associated with ELX-TEZ-IVA and 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 adjusted disease management costs for hospital visits and pharmacotherapy for patients receiving *CFTR* modulators, but because the cited studies did not indicate whether they controlled for patient $ppFEV_1$, the magnitude of potential cost savings is uncertain and may have been double counted. • The sponsor included a treatment-specific utility increment to account for the effect of treatment with ELX-TEZ-IVA beyond its impact mediated via $ppFEV_1$ and pulmonary exacerbations. The increment calculated by the sponsor was adjusted for $ppFEV_1$ but not for pulmonary exacerbations, and thus likely leads to double counting of benefits with ELX-TEZ-IVA. • The survival benefit with ELX-TEZ-IVA was overestimated, and the model estimates of median survival did not meet face validity.
CADTH reanalysis results	CADTH conducted a reanalysis that included the removal of an additional benefit of ELX-TEZ-IVA, LUM-IVA, and IVA on the long-term rate of decline in $ppFEV_1$ and pulmonary exacerbations; the removal of dynamic pricing; the inclusion of health care–related costs for patients on *CFTR* modulators in the period for which they achieved survival benefits compared with BSC; the removal of an adjustment to drug acquisition costs by patient compliance; the equating of hospital and pharmacotherapy costs; and the removal of a treatment-specific utility increment for patients on ELX-TEZ-IVA. • F/F genotype ◦ ICER vs. BSC = $1,434,435 per QALY ◦ ICER vs. LUM/IVA = $680,560 per QALY • F/MF genotype ◦ ICER vs. BSC = $1,653,605 per QALY • F/RF genotype ◦ ICER vs. BSC = $2,437,481 per QALY • F/G genotype (including F/R117H) ◦ ICER vs. BSC = $1,531,443 per QALY ◦ ICER vs. IVA = $622,381 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.
Key scenario analyses	The key scenario assessing the cost-effectiveness of ELX-TEZ-IVA in the full Health Canada population resulted in ICERs ranging from $1,129,990 to $1,868,095 per QALY compared with BSC; ELX-TEZ-IVA is not cost-effective at the submitted price.

BSC = best supportive care; BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ELX- = elexacaftor; ICER = incremental cost-effectiveness ratio; IVA = ivacaftor; LUM = lumacaftor; $ppFEV_1$ = 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, which included the anticipated market uptake of ELX-TEZ-IVA was underestimated; drug acquisition costs were adjusted by patient compliance, which is not appropriate; and there is uncertainty with the proportion of patients who would be eligible for public coverage of ELX-TEZ-IVA. The CADTH reanalysis included increasing the market uptake of ELX-TEZ-IVA in all 3 years of the time horizon and removing the adjustment of costs for patient compliance. Based on the CADTH reanalyses, the budget impact of introducing ELX-TEZ-IVA in patients with CF aged 6 to 11 years is expected to be $75,400,782 in year 1, $75,841,648 in year 2, and $76,845,222 in year 3, with a 3-year total of $228,087,652. The model is sensitive to the proportion of patients eligible for public drug coverage, as well as 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. The previous CADTH review of ELX-TEZ-IVA in patients older than 12 years estimated a budget impact of $1,279,931,452. Because the budget impact submitted for this review is specifically for the population between 6 and 11 years of age, the 3-year budget impact for the reimbursement of ELX-TEZ-IVA for patients with CF aged 6 years and older is expected to be $1,508,019,104.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: April 28, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None