

Reimbursement Recommendation

Vanzacaftor-Tezacaftor- Deutivacaftor (Alyftrek)

Indication: For the treatment of cystic fibrosis in patients aged 6 years and older who have at least one F508del mutation or another responsive mutation in the *CFTR* gene

Sponsor: Vertex Pharmaceuticals (Canada) Incorporated

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Alyftrek?

Canada's Drug Agency (CDA-AMC) recommends that Alyftrek be reimbursed by public drug plans for the treatment of cystic fibrosis (CF) in patients aged 6 years or older who have at least one F508del mutation or another responsive mutation in the *CFTR* gene (identified in [Table 1](#) of this document), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Alyftrek should only be covered to treat patients aged 6 years or older who have a confirmed diagnosis of CF with at least 1 of the eligible *CFTR* gene mutations.

What Are the Conditions for Reimbursement?

Alyftrek should only be reimbursed if prescribed by specialists in the treatment of CF and if the cost of Alyftrek does not exceed the total cost of other triple-combination *CFTR* modulator therapies (e.g., elexacaftor-tezacaftor-ivacaftor [ELX-TEZ-IVA] [Trikafta]). Alyftrek should not be reimbursed in combination with other *CFTR* modulator therapies.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials in patients with CF aged at least 12 years demonstrated that 52 weeks of Alyftrek treatment has little to no difference in clinical outcomes that are important to patients compared to Trikafta. These outcomes include lung function, pulmonary exacerbations, nutritional status, health-related quality of life (HRQoL), and serious adverse events (SAEs). Evidence from 1 clinical trial showed that Alyftrek treatment may have clinical benefits in patients with CF aged 6 to 11 years.
- For the rare *CFTR* mutations that have not been evaluated in clinical trials (i.e., those for which the response to Alyftrek has only been assessed in a laboratory), the committee acknowledged the practical challenges with generating clinical evidence. The committee concluded that Alyftrek has the potential to provide clinically meaningful benefit to patients with CF caused by rare *CFTR* mutations, on the basis that the laboratory data were considered acceptable by Health Canada and that the biological plausibility of a beneficial treatment effect was supported by the CF specialists who provided input for this review.
- Alyftrek is expected to offer similar clinical benefits to Trikafta and serve as an alternative for patients who cannot tolerate Trikafta. Alyftrek is

Summary

approved for a broader range of CF-causing mutations than Trikafta. However, some patients still have CF-causing mutations that neither drug can treat, or they may not tolerate these drugs.

- Based on the CDA-AMC assessment of the health economic evidence, Alyftrek does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Alyftrek compared with Trikafta.
- Based on public list prices, Alyftrek is estimated to cost the public drug plans approximately \$68 million over the next 3 years. The actual budget impact is uncertain and will depend on the uptake of Alyftrek, the confidential price of Trikafta, and the proportion of patients who have public drug plan coverage.

Additional Information

What Is CF?

CF is a rare genetic condition that results in airway obstruction and eventual loss of lung function. It is the most common fatal genetic disease affecting children and young adults in Canada. Approximately 4,513 people in Canada were living with CF in 2023.

Unmet Needs in CF

CF is caused by a variety of different mutations in the *CFTR* gene, and not all of these mutations are responsive to the currently available medications. Trikafta is the current standard of care, and patients who are not eligible for or are unable to tolerate Trikafta currently do not have access to another triple-combination *CFTR* modulator.

How Much Does Alyftrek Cost?

Treatment with Alyftrek is expected to cost \$322,151 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that vanzacaftor-tezacaftor-deutivacaftor (VNZ–TEZ–D-IVA) be reimbursed for the treatment of CF in patients aged 6 years or older who have at least one F508del mutation or another responsive mutation in the *CFTR* gene (listed in [Table 1](#)) only if the conditions listed in [Table 2](#) are met.

Rationale for the Recommendation

Two double-blind, noninferiority, randomized controlled trials (RCTs), the SKYLINE 102 trial (N = 405) and SKYLINE 103 trial (N = 574), demonstrated with high-certainty evidence that treatment with VNZ–TEZ–D-IVA results in little to no difference in change in lung function (measured using percent predicted forced expiratory volume in 1 second [ppFEV₁]) when compared to ELX-TEZ-IVA through 52 weeks of treatment in patients aged at least 12 years with CF who had at least one F508del mutation or another responsive *CFTR* gene mutation. There was also moderate to high-certainty evidence demonstrating little to no difference between the treatment groups for several other clinically important outcomes: the rate of pulmonary exacerbations, body mass index (BMI), BMI z score in patients aged 20 years or younger, HRQoL measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory domain score, the number of patients who experienced events of elevated transaminases, and the number of patients with SAEs. One single-arm study (the RIDGELINE study, with cohorts A1 [N = 17] and B1 [N = 78]) of VNZ–TEZ–D-IVA, which included patients aged 6 to 11 years with CF and ELX-TEZ-IVA-responsive *CFTR* gene mutations, reported little change from baseline at week 24 in the outcomes of ppFEV₁, BMI, BMI z score, and CFQ-R Respiratory domain score; however, the certainty of the evidence compared to ELX-TEZ-IVA or any other comparator was very low owing to the noncomparative design of the study. Nonetheless, the efficacy and safety profile appeared to be consistent with that observed in the RCTs, and it was supportive of extrapolation of the RCT results in this age group.

CDEC noted that in vitro data from 4 nonclinical studies were considered acceptable evidence by Health Canada to support the use of VNZ–TEZ–D-IVA in patients with rare *CFTR* gene mutations not assessed in the clinical trials. The inclusion of *CFTR* mutations without clinical evidence in the approved indication was based primarily on biological plausibility and was supported by the CF specialists who provided input for this review. Given the rarity of these mutations, the committee acknowledged the practical challenges with generating clinical evidence. CDEC concluded that VNZ–TEZ–D-IVA has the potential to provide clinically meaningful benefit to those patients who have *CFTR* mutations that have been shown to be responsive to ELX-TEZ-IVA.

Patients identified a need for an effective treatment that prolongs life, improves quality of life, has less frequent dosing, and can be used in patients who are ineligible for or are unable to tolerate ELX-TEZ-IVA, the standard of care. CDEC concluded that VNZ–TEZ–D-IVA meets some of the needs identified by patients, including offering similar clinical benefits and a broader range of *CFTR* gene mutation coverage compared to ELX-TEZ-IVA, and serving as an alternative for patients who do not tolerate ELX-TEZ-IVA, but there remains

an unmet need in patients whose CF-causing mutations are not included in either indication or who do not tolerate either of these therapies. A patient group suggested that the once-daily dosing of VNZ–TEZ–D-IVA may improve treatment adherence in a minority of patients for whom the twice-daily dosing of ELX-TEZ-IVA is burdensome, which may be a more prevalent issue in pediatric patients. However, there is no evidence to support its effects on adherence, so this remains uncertain.

At the sponsor-submitted price for VNZ–TEZ–D-IVA and publicly listed price for all other drugs, VNZ–TEZ–D-IVA was more costly than ELX-TEZ-IVA. As the effectiveness of VNZ–TEZ–D-IVA is considered similar to that of ELX-TEZ-IVA, the total drug cost of VNZ–TEZ–D-IVA should not exceed the total drug cost of ELX-TEZ-IVA.

Table 1: *CFTR* Mutations Listed as Responsive to VNZ–TEZ–D-IVA in the Health Canada Product Monograph

<i>CFTR</i> mutations							
Based on clinical data							
A455E	G1244E	H1054D	L1077P	R1066H	S1159F	S549R	W1282R
D1152H	G551D	I336K	L206W	R347P	S1251N	S945L	Y563N
F508del	G85E	I502T	M1101K	R352Q	S549N	W1098C	—
Based on in vitro data							
1507_151 5del9	D443Y; G576A; R668C	F587I	H1085R	L137P	Q1313K	R347L	T1086I
2183A- > G	D513G	G1047R	H1375P	L1480P	Q237E	R352W	T1246I
3141del9	D565G	G1061R	H139R	L15P	Q237H	R516G	T1299I
3195del6	D579G	G1069R	H199R	L165S	Q359R	R516S	T338I
3199del6	D614G	G1123R	H199Y	L333F	Q372H	R555G	T351I
546insCT A	D924N	G1247R	H609R	L333H	Q452P	R560S	T604I
A1006E	D979V	G1249R	H620P	L346P	Q493R	R560T	V1153E
A1067P	D993Y	G126D	H939R; H949L	L441P	Q552P	R74Q	V1240G
A1067T	E116K	G1349D	I105N	L453S	Q98R	R74W	V1293G
A107G	E116Q	G149R	I1139V	L619S	R1048G	R74W; D1270N ⁴	V201M
A120T	E193K	G178R	I1234Vdel 6aa	M1101R	R1066C	R74W;V201M; D1270N	V232D
A234D	E292K	G194R	I1269N	M1137V	R1066L	R74W; V201M	V392G
A309D	E474K	G194V	I1366N	M150K	R1066M	R751L	V456A

CFTR mutations							
A349V	E56K	G27E	I1398S	M265R	R1070Q	R75L	V456F
A46D	E588V	G27R	I148N	M952I	R1070W	R933G	V520F
A554E	E60K	G314E	I331N	M952T	R117C	S1045Y	V603F
A559T	E822K	G424S	I506L	N1088D	R117C; G576A; R668C	S108F	W361R
A559V	E92K	G463V	I506T	N1303I	R117G	S1118F	Y1014C
A561E	F1016S	G480C	I601F	N1303K	R117H	S1159P	Y1032C
A613T	F1052V	G480S	I618T	N186K	R117L	S1255P	Y109N
A62P	F1074L	G551A	I980K	N187K	R117P	S13F	Y161D
A72D	F1099L	G551S	K1060T	P205S	R1283M	S341P	Y161S
C491R	F1107L	G576A; R668C	K162E	P574H	R1283S	S364P	Y569C
D110E	F191V	G622D	K464E	P5L	R258G	S492F	Y913C
D110H	F200I	G628R	L1011S	P67L	R297Q	S549I	—
D1270N	F311del	G91R	L102R	P750L	R31L	S737F	—
D1445N	F311L	G970D	L1065P	P99L	R334L	S912L	—
D192G	F508C; S1251N	G970S	L1324P	Q1100P	R334Q	S977F	—
D443Y	F575Y	H1085P	L1335P	Q1291R	R347H	T1036N	—
Based on extrapolation							
1898 + 3A→G	2789 + 5G→A	3272 to 26A→G	3849 + 10k bC→T	3849 + 4A→G	4005 + 2T→C	5T;TG13	711 + 3A→G
2789 + 2ins A	3041- 15T→G	3600G→A	3849 + 40A→G	3850- 3T→G	5T;TG12	621 + 3A→G	E831X

VNZ-TEZ-D-IVA = vanzacaftor-tezacaftor-deutivacaftor.

Source: VNZ-TEZ-D-IVA Health Canada product monograph (authorization date: July 21, 2025).

Table 2: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Confirmed diagnosis of CF with at least 1 of the mutations in the <i>CFTR</i> gene listed in Table 1 of this document 2. Aged 6 years or older	Clinical evidence supports that VNZ-TEZ-D-IVA has a comparable clinical benefit to ELX-TEZ-IVA in this patient population. The indication approved by Health Canada for VNZ-TEZ-D-IVA is limited to patients with at least 1 mutation in the <i>CFTR</i> gene that has been shown to be responsive to VNZ-TEZ-D--	Table 1 lists the 266 <i>CFTR</i> gene mutations that are identified as responsive to VNZ-TEZ-D-IVA in the Health Canada product monograph based on clinical data, in vitro data, and/or extrapolation. <i>CFTR</i> genetic testing is standard of

Reimbursement condition	Reason	Implementation guidance
	IVA based on clinical data, in vitro data, and/or extrapolation. The pivotal trials enrolled patients aged 6 to 11 (in the RIDGELINE trial), and patients aged 12 and older (in the SKYLINE 102 and SKYLINE 103 trials).	care and part of the routine diagnostic framework to confirm CF. No implementation barriers due to testing are anticipated from the testing as part of establishing treatment eligibility for VNZ–TEZ–D-IVA.
3. The following measurements must be completed before initiating treatment with VNZ–TEZ–D-IVA: 3.1. baseline spirometry measurements of FEV₁ in litres and percent predicted (baseline lung function should be measured within a 3-month period before beginning treatment with VNZ–TEZ–D-IVA) 3.2. number of days treated with oral and IV antibiotics for pulmonary exacerbations in the previous 6 months or number of pulmonary exacerbations requiring oral and/or IV antibiotics in the previous 6 months 3.3. number of CF-related hospitalizations in the previous 6 months 3.4. weight, height, and BMI 3.5. CFQ-R Respiratory domain score.	This must be done to establish baseline values to be used for renewal of reimbursement for treatment with VNZ–TEZ–D-IVA.	Weight, height, and BMI for pediatric patients are collected and reported as z scores or percentiles in clinical practice in Canada. 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 aged at least 14 years (CFQ-R teen or adult version).
Renewal		
4. For the first renewal in patients who have not previously received a CFTRm therapy: the physician must provide at least 1 of the following to demonstrate benefit after 6 months of treatment with VNZ–TEZ–D-IVA: 4.1. improvement of lung function by 5% of predicted or more, at 6 months relative to baseline 4.2. a decrease in the total number of days for which the patient received	The studies demonstrated that, compared to ELX-TEZ-IVA, treatment with VNZ–TEZ–D-IVA was associated with similar benefits in improving lung function (ppFEV ₁), nutritional status (BMI or BMI z score), health-related quality of life (CFQ-R Respiratory domain scores), and reducing the rate of pulmonary exacerbations, including events that required IV antibiotics and/or hospitalization.	Clinically significant improvements from baseline in lung function (ppFEV₁) 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

Reimbursement condition	Reason	Implementation guidance
treatment with oral and/or IV antibiotics for pulmonary exacerbations in the previous 6 months 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 in the previous 6 months compared with the 6-month period before initiating treatment 4.3. no decline in BMI (BMI z score in children) at 6 months compared with the baseline BMI (or BMI z score) assessment 4.4. decreased number of CF-related hospitalizations at 6 months compared with the 6-month period before initiating treatment 4.5. improvement by 4 points or more in the CFQ-R Respiratory domain score at 6 months compared to baseline.		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).
5. For the first renewal in patients who switch from a CFTRm to VNZ-TEZ-D-IVA: the physician must provide at least 1 of the following to demonstrate benefit after 6 months of treatment with VNZ-TEZ-D-IVA: 5.1. no decline in lung function at 6 months relative to baseline before the switch to VNZ-TEZ-D-IVA 5.2. no increase in the total number of days for which the patient received treatment with oral and/or IV antibiotics for pulmonary exacerbations in the previous 6 months compared with the 6-month period before initiating treatment, or	Demonstration of further improvements from baseline in patients who switch from 1 CFTRm (e.g., ELX-TEZ-IVA) to VNZ-TEZ-D-IVA may not be possible. Clinical expert input indicated that stability of CF management is the goal in patients switching from 1 CFTRm to another and that renewal of reimbursement is reasonable upon maintenance of the benefits previously observed on the other CFTRm therapy.	Based on clinical expert consultation, patients who do not meet the renewal criteria for VNZ-TEZ-D-IVA after switching from another CFTRm may switch back to the previous therapy if considered appropriate by their treating clinician.

Reimbursement condition	Reason	Implementation guidance
no increase in the total number of pulmonary exacerbations requiring oral and/or IV antibiotics in the previous 6 months compared with the 6-month period before initiating treatment 5.3. no decline in BMI (BMI z score in children) at 6 months compared with the baseline BMI (or BMI z score) assessment 5.4. no increase in the number of CF-related hospitalizations at 6 months compared with the 6-month period before initiating treatment 5.5. no reduction in the CFQ-R Respiratory domain score at 6 months compared with baseline measurement.		
6. The physician must provide evidence of continued clinical benefit from VNZ–TEZ–D-IVA for subsequent renewal of reimbursement. Subsequent renewal should be assessed every 12 months.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Discontinuation		
7. The patient has undergone lung transplant.	Patients who had had a solid organ transplant were excluded from the main studies of VNZ–TEZ–D-IVA, and clinical experts in Canada indicated that the treatment should be discontinued in patients who have received lung transplant.	—
Prescribing		
8. Prescribing of VNZ–TEZ–D-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.	—
9. VNZ–TEZ–D-IVA should not be reimbursed in combination with other <i>CFTR</i> modulators.	There is no evidence for the use of VNZ–TEZ–D-IVA in combination with other available <i>CFTR</i> modulators.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
10. The total cost of VNZ–TEZ–D-IVA should be negotiated so that it does not exceed the total cost of ELX-TEZ-IVA.	Based on the clinical evidence submitted by the sponsor, VNZ–TEZ–D-IVA is expected to produce similar health outcomes as ELX-TEZ-IVA. As such, there is insufficient evidence to justify a cost premium for VNZ–TEZ–D-IVA over the least expensive <i>CFTR</i> modulator reimbursed for CF in people aged 6 years and older who have at least one F508del mutation or another responsive mutation in the <i>CFTR</i> gene.	—
Feasibility of adoption		
11. The feasibility of adoption of VNZ–TEZ–D-IVA must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

BMI = body mass index; CDA-AMC = Canada's Drug Agency; CF = cystic fibrosis; *CFTR*m = *CFTR* modulator; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; ppFEV₁ = percent predicted forced expiratory volume in 1 second; TEZ = tezacaftor; VZN = vanzacaftor.

Discussion Points

- Significant unmet need:** CDEC deliberated on VNZ–TEZ–D-IVA considering the criteria for significant unmet need that are described in the CDA-AMC Procedures for Reimbursement Reviews. CF is a rare, genetic, incurable, life-limiting disease that causes substantial morbidity and mortality. The current standard of care, ELX-TEZ-IVA, is approved for 153 *CFTR* gene mutations in Canada. CDEC noted that rare and unclassified *CFTR* mutations not included in the ELX-TEZ-IVA indication are disproportionately found in racialized individuals, but it is unknown to what degree the availability of VNZ–TEZ–D-IVA would address the unmet need in these individuals. Patients ineligible for ELX-TEZ-IVA currently do not have access to a triple-combination *CFTR* modulator.
- Access to *CFTR* modulators by genotype:** CDEC noted that the available evidence reasonably suggests that VNZ–TEZ–D-IVA may reduce morbidity and/or mortality to a similar extent as ELX-TEZ-IVA in patients with CF, and would therefore meet a significant unmet need for patients whose CF-causing mutations are included in the VNZ–TEZ–D-IVA indication (currently 266 mutations) but are not included in the ELX-TEZ-IVA indication (currently 153 mutations). All of the mutations included in the ELX-TEZ-IVA indication are also included in the VNZ–TEZ–D-IVA indication except for 1, and the VNZ–TEZ–D-IVA indication encompasses 113 more CF-causing mutations than ELX-TEZ-IVA in total. VNZ–TEZ–D-IVA would also serve as an alternative for patients who are unable to tolerate ELX-TEZ-IVA. The committee concluded that VNZ–TEZ–D-IVA would meet important unmet needs in some patients with CF, but that there would be remaining significant unmet needs among patients for whom neither ELX-TEZ-IVA nor VNZ–TEZ–D-IVA are indicated, or who are unable to tolerate both therapies, which have similar mechanisms of action.

- **Potential unmet need (dosing regimen):** CDEC discussed the clinical expert input that the once-daily dosing of VNZ–TEZ–D-IVA may improve treatment adherence in a minority of patients who find the twice-daily dosing of ELX-TEZ-IVA burdensome. Patients with CF generally require many concurrent medications in addition to treatment with *CFTR* modulators; therefore, the majority of patients with CF may not see a significant difference in adherence. No evidence was provided to suggest a beneficial effect on adherence; hence, the effects of once-daily dosing are unknown. CDEC also discussed that the once-daily dosing of VNZ–TEZ–D-IVA may provide less flexibility for dose reduction in patients experiencing an adverse event (AE) compared to ELX-TEZ-IVA dosed twice daily.
- **Evidence for the pediatric population aged 6 to 11 years:** The committee discussed the very low certainty of the clinical study evidence from the noncomparative RIDGELINE study, which provided data for patients aged 6 to 11 years (inclusive). Results from the RIDGELINE study were consistent with the change from baseline observations in the SKYLINE 102 and SKYLINE 103 RCTs, which is supportive of extrapolating the conclusion of similar clinical benefit between VNZ–TEZ–D-IVA and ELX-TEZ-IVA in this age group. Also supportive of this conclusion are the similarities in mechanism of action (biological plausibility) and the precedence of use of ELX-TEZ-IVA in this age group.
- **Evidence gap:** The committee noted that all patients enrolled in the pivotal trials had prior exposure to ELX-TEZ-IVA and/or participated in run-in periods with ELX-TEZ-IVA treatment. There is a gap in the evidence regarding patients who are naive to *CFTR* modulators. CDEC noted that this is expected to be a small proportion of patients, given that the majority of patients are currently receiving ELX-TEZ-IVA in clinical practice and that there is precedence for the use of ELX-TEZ-IVA (which has a similar mechanism of action) in *CFTR* modulator-naïve patients with CF.
- **Clinical relevance of sweat chloride:** The committee noted that there was a small reduction in sweat chloride (SwCl) in the VNZ–TEZ–D-IVA group relative to the ELX-TEZ-IVA group and deliberated on its potential clinical significance. CDEC noted that SwCl is an important marker in CF and that it has utility in providing mechanistic and pharmacodynamic information, such as for diagnosis and whether a patient or an in vitro analysis of a mutation model is responding to *CFTR* modulator therapy. However, the clinical importance of SwCl reductions beyond that previously seen in studies of ELX-TEZ-IVA has not been clearly established. There is currently no robust evidence that an additional reduction in SwCl is associated with additional clinical benefits compared to ELX-TEZ-IVA, nor that further reduction in SwCl is an appropriate marker or specifically correlated with any patient-relevant clinical end points at this time. The clinical experts also stated that SwCl is not routinely measured in clinical practice.
- ***CFTR* mutations without clinical evidence:** The committee discussed the use of in vitro evidence to support the indication of VNZ–TEZ–D-IVA for mutations not feasible to include in clinical trials due to their rarity, which is inherently more uncertain but follows the precedent set in the evaluations of ELX-TEZ-IVA, has adequate biological rationale, and is accepted by regulatory bodies such as Health Canada. CDEC also noted that there are known CF-causing mutations that lack response to available *CFTR* modulators.

- **Testing procedure:** The committee acknowledged that genetic testing for CF is standard procedure and that the availability of VNZ–TEZ–D-IVA is not expected to impact the frequency of genetic testing.
- **Uncertainty in the economic analysis:** The cost-effectiveness estimates for VNZ–TEZ–D-IVA versus ELX-TEZ-IVA are highly uncertain. The difference in quality-adjusted life-years (QALYs) in the CDA-AMC base case in favour of VNZ–TEZ–D-IVA (0.13) was primarily due to differences in the rate of treatment discontinuation between treatments. Findings from the submitted head-to-head trials suggest that VNZ–TEZ–D-IVA likely results in little to no difference in clinically important outcomes versus ELX-TEZ-IVA. Therefore, the finding of any difference in QALYs between VNZ–TEZ–D-IVA and ELX-TEZ-IVA is highly uncertain.
- **Uncertainty in the budget impact:** The budget impact of reimbursing VNZ–TEZ–D-IVA for the indicated population is estimated to be approximately \$68 million over the first 3 years of reimbursement compared to the amount currently spent on ELX-TEZ-IVA. The actual budget impact will depend on the uptake of VNZ–TEZ–D-IVA, the confidential price of ELX-TEZ-IVA, and the proportion of patients who have public drug plan coverage.

Background

CF, a rare autosomal recessive condition, is the most common fatal genetic disease affecting children and young adults in Canada. It is caused by mutations in the *CFTR* gene. The Canadian Cystic Fibrosis Registry reported that there were 4,513 people in Canada living with CF in 2023. Of these, 87.8% carried 1 or more F508del mutations. CF results in airway obstruction, chronic endobronchial infection, and inflammation, which ultimately lead to destruction of lung tissue through development of bronchiectasis and loss of lung function. Lung disease accounts for the vast majority (> 80%) of deaths in patients with CF. Gastrointestinal and pancreatic involvement results in pancreatic exocrine insufficiency in most individuals with CF, causing malabsorption of fats and fat-soluble vitamins, which leads to malnutrition. With increasing age, patients with CF-related pancreatic insufficiency may develop CF-related diabetes and require treatment with insulin (32.5% of adults and 2.4% of children living with CF in Canada in 2024).

VNZ–TEZ–D-IVA is indicated for the treatment of CF in patients aged 6 years and older who have at least one F508del mutation or another responsive mutation in the *CFTR* gene. In the Health Canada notice of compliance, 266 *CFTR* gene mutations were approved as part of the indication based on clinical data, in vitro data, and extrapolation. This represents an expansion from the 153 *CFTR* gene mutations approved for ELX-TEZ-IVA in Canada.

CFTR genetic testing is standard of care and part of the routine diagnostic framework to confirm CF. No implementation barriers due to testing are anticipated from the testing as part of establishing treatment eligibility for VNZ–TEZ–D-IVA.

VNZ–TEZ–D-IVA is a *CFTR* modulator. It is available as oral tablets in 2 doses: 4 mg VNZ, 20 mg TEZ, and 50 mg D-IVA; and 10 mg VNZ, 50 mg TEZ, and 125 mg D-IVA. The recommended dosage for patients who

weigh less than 40 kg is 3 of the 4/20/50 mg tablets once daily, and for patients who weigh at least 40 kg, it is 2 tablets of the 10/50/125 mg tablets once daily.

Sources of Information Used by the Committee

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

- a review of 2 RCTs in patients with CF aged at least 12 years; 1 nonrandomized study in patients with CF aged 6 to 11 years; and 4 nonclinical in vitro studies assessing response to treatment using cell models of CF-causing mutations
- patients' perspectives gathered by 1 patient group, Cystic Fibrosis Canada
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with CF
- input from 1 clinician group, the Cystic Fibrosis Canada Health Care Advisory Council
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group, Cystic Fibrosis Canada, submitted input for this review. Information was gathered through focus groups in people in Canada with CF and their caregivers. Other sources of data included surveys (including a 2021 survey with more than 1,200 responses, data from the Canadian Cystic Fibrosis Registry, a multiphase burden of disease study, and other relevant publications).

The patient group highlighted that patients not taking *CFTR* modulators frequently have periods of infection and acute inflammation called exacerbations that require a hospital stay of at least 2 weeks and may last up to 4 weeks. Some of these patients could benefit from *CFTR* modulators, but there may not currently be *CFTR* modulator therapies with a Health Canada indication for their mutation. The group noted that approximately 33% of all adult patients with CF in Canada have CF-related diabetes. Any of the other drugs that patients need to take on a regular basis also have negative side effects and long-term risks, such as chronic use of antibiotics that may lead to resistance. Moreover, as patients age, they may need to try multiple antibiotics to find 1 that works, making management of drug-to-drug interactions difficult. The patient group reiterated that currently, only *CFTR* modulators target the underlying pathophysiology of CF by improving the function of *CFTR*, while other therapies used to treat CF are for the management of complications and control of symptoms.

The patient group highlighted that too many patients lack access to any *CFTR* modulators, including those who have ultrarare mutations that are not on the narrow list of 152 mutations indicated for ELX-TEZ-IVA or who cannot tolerate it, or those that only respond to VNZ-TEZ-D-IVA. The patient group noted that the US

FDA has approved the use of ELX-TEZ-IVA in 272 mutations, compared to 152 mutations in Canada; the group suggested that there are approximately 23 patients in Canada with 1 or more of the 119 mutations that lack ELX-TEZ-IVA approval who could access ELX-TEZ-IVA in the US at the age of 2 years or older, but cannot access ELX-TEZ-IVA in Canada. Additionally, VNZ-TEZ-D-IVA had been approved by the FDA for an additional 31 unique mutations for which ELX-TEZ-IVA is not approved; this represents approximately 13 additional Canadians without access to ELX-TEZ-IVA. The group pointed out that, if VNZ-TEZ-D-IVA gets approved in Canada, as many as 36 individuals could access it at the age of 6 years or older for the first time. The group specifically requested that the committee recommend access to VNZ-TEZ-D-IVA for the 152 *CFTR* mutations currently indicated for ELX-TEZ-IVA and 151 rare mutations or mutation combinations indicated by the FDA for VNZ-TEZ-D-IVA that are currently not eligible for reimbursement of *CFTR* modulator therapy in Canada, and to recommend the broadest possible access to VNZ-TEZ-D-IVA for individuals with other *CFTR* mutations for which there is evidence and for which more evidence is being generated over time (including in vitro laboratory evidence or clinical evidence) showing that they will or may respond to this therapy. The group highlighted that CF has significant financial implications for patients and their caregivers, health systems, and society.

No patients reported experience with VNZ-TEZ-D-IVA treatment. The patient group highlighted that VNZ-TEZ-D-IVA may improve quality of life and adherence as a 1-pill-a-day treatment, which would provide parents with an option who may have difficulty administering medications to their children who already take several medications a day to maintain their health.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts noted that ELX-TEZ-IVA is the current standard of care in patients with CF aged 6 years and older with eligible CF-causing mutations, but there is an unmet need for more effective therapies that prolong life; improve quality of life; and reduce the treatment burden of supportive medications in patients whose CF-causing mutations are not eligible for treatment with ELX-TEZ-IVA, which represents approximately 10% of patients with CF in Canada and disproportionately represents racialized people. Additionally, even among patients eligible for treatment with ELX-TEZ-IVA, the clinical experts noted that most patients still have SwCI values in an abnormal range. Doses of ELX-TEZ-IVA are taken twice daily and require fat-containing meals for absorption; ergo, the experts noted that less frequent dosing is an unmet need that might improve adherence. Some patients may experience AEs or intolerances to ELX-TEZ-IVA requiring cessation of treatment, and there is an unmet need for alternative triple-combination *CFTR* modulator therapies in those circumstances. Finally, overall pill and treatment burden remains high in patients with CF despite reductions after the advent of triple-combination *CFTR* modulator therapies (i.e., ELX-TEZ-IVA).

The clinical experts consulted by CDA-AMC stated that VNZ-TEZ-D-IVA would occupy a similar place in therapy to ELX-TEZ-IVA, with the caveat that it may be applicable to a wider range of mutations, and that the current Health Canada indications begin at different ages (i.e., ELX-TEZ-IVA is currently indicated for patients aged at least 2 years, while VNZ-TEZ-D-IVA is indicated for patients aged at least 6 years). The

experts noted that, given the once-daily dosing of VNZ–TEZ–D-IVA, there may be expected improvements in treatment adherence compared to ELX-TEZ-IVA. However, patients with CF typically take numerous pills daily in addition to *CFTR* modulator therapies, so this may not represent a substantial difference in overall treatment or pill burden. Nonetheless, 1 expert specialized in pediatric care said that this may be particularly significant for the treatment of pediatric patients with CF. The experts noted that it may be premature to switch to VNZ–TEZ–D-IVA for every patient currently stable on ELX-TEZ-IVA, due to the longer clinical safety record of ELX-TEZ-IVA; however, VNZ–TEZ–D-IVA is generally expected to become the new standard of care for eligible patients. Additionally, if there are clinical signals that reaching a lower SwCI level than what was previously attained with ELX-TEZ-IVA results in less end-organ damage, it may further shift treatment paradigms and reduce the need for other supportive therapies.

The clinical experts indicated that the patient population appropriate for treatment with VNZ–TEZ–D-IVA is similar to that of ELX-TEZ-IVA, with the exception that there may be additional CF-causing mutations eligible for treatment with VNZ–TEZ–D-IVA. Aside from genotype, the patient population is expected to be similar.

The clinical experts noted that assessment of CF-related treatment is based on lung function spirometry, number of days treated with oral and IV antibiotics for pulmonary exacerbations, number of CF-related hospitalizations, and monitoring of BMI or BMI z score (as appropriate by age) for signs of malnutrition. The clinical experts informed CDA-AMC that the assessments related to VNZ–TEZ–D-IVA should be similar to those expected for ELX-TEZ-IVA, although it is also important to consider in any reimbursement criteria that assessments for initiation, continuation, or discontinuation should differ for patients newly starting triple-combination *CFTR* modulators (i.e., generally greater expected improvements with therapy) versus switching between triple-combination *CFTR* modulators (i.e., expected to maintain the benefit previously observed with the other therapy). Assessment of response in these metrics should generally be performed after a year of treatment, as the experts highlighted that some metrics (especially pulmonary exacerbations and BMI or BMI z score) may have fluctuations with seasonal illness and short-term instability in pediatric patients that may not be reflective of the effect of the drug.

The clinical experts noted that discontinuation should be considered in the case of intolerable AEs that cannot be sufficiently managed or in the case of lung transplant, similar to current practice with ELX-TEZ-IVA (although this does not reflect a contraindication specified by Health Canada).

The clinical experts noted that a physician practising within or under the directed supervision of a Canadian CF clinic should manage the prescription and renewal of VNZ–TEZ–D-IVA.

Clinician Group Input

One clinician group, the Cystic Fibrosis Canada Health Care Advisory Council, provided input for this review. Information for this submission was gathered through experience gained by working with and delivering medical services to people with CF; consultations with people with CF who are not eligible for ELX-TEZ-IVA; a review of medical and scientific literature, including clinical trial results and real-world experience; and the Canadian Cystic Fibrosis Registry, a collection of patient data and other information regarding CF care and outcomes. Two clinicians submitted input for this review.

The input from the clinician group was generally consistent with the clinical experts consulted for this review, emphasizing that about 10% of patients have mutations not currently approved for treatment with available *CFTR* modulators in Canada, and that there are no alternative triple-combination *CFTR* modulators for patients with intolerances to ELX-TEZ-IVA. The group agreed that the once-daily regimen of VNZ-TEZ-D-IVA may improve adherence and convenience compared to the twice-daily regimen of ELX-TEZ-IVA.

The group noted that rare mutations for which there are currently no *CFTR* modulator indications are disproportionately found in racialized communities, so expanded access to this therapy may improve equitable access to disease-modifying treatments in Canada.

The clinician group noted that, according to recent Canadian clinical guidelines, all patients with CF who have at least 1 *CFTR* modulator-responsive *CFTR* variant should be treated with a *CFTR* modulator. The clinician group noted that patients with CF best suited for the drug under review include patients already taking ELX-TEZ-IVA who are experiencing challenges due to side effects or related to treatment adherence on a twice-daily regimen, and patients with rare mutations that are not approved for treatment with ELX-TEZ-IVA but may respond to VNZ-TEZ-D-IVA. The group agreed with the clinical experts regarding the metrics and yearly time frame of reassessments for treatment efficacy, as well as factors to consider for treatment discontinuation and prescribing.

Drug Program Input

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

- considerations for:
 - initiation of therapy
 - continuation or renewal of therapy
 - discontinuation of therapy
 - prescribing of therapy
 - care provision issues
 - system and economic issues.

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

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Consider alignment with the most recent reimbursement criteria for Trikafta (ELX-TEZ-IVA) as appropriate, for those aged 6 years or older.	The committee and clinical experts agreed that this criterion should be aligned with that of Trikafta for patients aged 6 years or older.
Considerations for continuation or renewal of therapy	
Consider alignment with the most recent reimbursement criteria for Trikafta as appropriate, for those aged 6 years or older.	The committee agreed with clinical expert input that this criterion should be aligned with that of Trikafta for patients aged 6 years or older, with the caveat that patients switching from 1 CFTRm to another should not be expected to have further improvements in outcomes in the same magnitude as patients who are first starting a CFTRm, but instead should be expected to have approximately equal or stable clinical status in CF-related outcomes and lung function.
Considerations for discontinuation of therapy	
Consider alignment with the most recent reimbursement criteria for Trikafta as appropriate, for those aged 6 years or older.	The committee agreed that this criterion should be aligned with that of Trikafta for patients aged 6 years or older.
Considerations for prescribing of therapy	
Is there evidence for the use of Alyftrek (VNZ-TEZ-D-IVA) in combination with other CFTRm therapies?	The committee stated that there is no evidence for the use of VNZ-TEZ-D-IVA in combination with other CFTRm therapies.
Consider alignment with the most recent reimbursement criteria for Trikafta as appropriate, for those aged 6 years or older.	The committee and clinical experts agreed that this criterion should be aligned with that of Trikafta for patients aged 6 years or older.
Care provision issues	
Clinical experts consulted in previous reviews (i.e., for Trikafta in November 2023) have noted that SwCl testing should not be used to evaluate response to treatment for the purposes of drug reimbursement because it is not clearly predictive of clinically important outcomes and only reflects the mechanism of action of CFTRm therapies. Clinical experts have also noted that access to SwCl testing can be challenging in some jurisdictions and that the timelines to receive the test results can fluctuate. They have also expressed concerns about the capacity of the health system to accommodate repeated SwCl testing. Should SwCl be used to assess response to treatment for the purposes of reimbursement? If so, under what circumstances?	The committee agreed that SwCl is not appropriate for evaluating response to treatment for the purposes of drug reimbursement due to the issues listed. As described by the clinical experts, SwCl is an important metric for diagnostics in CF and a decrease in SwCl reflects the mechanism of action of initiated CFTRm therapies, but it is too heterogeneous between patients (and may be misleading in some CF-causing mutations), and it has not been established as a clear surrogate for prediction of important clinical outcomes such as ppFEV₁. The clinical benefit and meaningfulness of an additional reduction in SwCl beyond that previously seen with ELX-TEZ-IVA has also not been established. Moreover, repeat SwCl testing in clinical practice may present a burden to the health system. However, the experts did consider SwCl an appropriate and sensitive end point for assessing whether a rare CF mutation without clinical evidence responds to CFTRm therapy and that repeat sweat testing may be warranted in the occasional patient with a rare genotype to demonstrate mechanistic response.

Implementation issues	Response
System and economic issues	
The sponsor has indicated that 98.7% of patients eligible for Alyftrek are also eligible for Trikafta. It is anticipated that Alyftrek will replace Trikafta for new patients initiating treatment and for existing patients currently receiving Trikafta, which has a budget impact. Do you agree Alyftrek is likely to replace Trikafta for patients initiating CFTRm therapy, and for patients currently receiving Trikafta?	The committee acknowledged clinical expert input that a majority of patients with CF receiving ELX-TEZ-IVA would likely switch to VNZ-TEZ-D-IVA. Out of all patients with CF in Canada, the experts predicted there would be approximately 60% to 70% of patients interested in initiating VNZ-TEZ-D-IVA.

CF = cystic fibrosis; CFTRm = *CFTR* modulator; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; ppFEV₁ = percent predicted forced expiratory volume in 1 second; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor.

Clinical Evidence

Systematic Review

Description of Studies

Two double-blind, phase III RCTs, the SKYLINE 102 trial (VX21-121-102, N = 405) and SKYLINE 103 trial (VX21-121-103, N = 574) were included. One single-arm, phase III study (the RIDGELINE study, VX21-121-105) was also included, specifically cohort A1 (N = 17) and cohort B1 (N = 78).

The RCTs were randomized studies with a 52-week treatment phase and were similar in study design. Both SKYLINE studies compared VNZ-TEZ-D-IVA to ELX-TEZ-IVA in patients with CF aged at least 12 years with ELX-TEZ-IVA-responsive mutations. Both studies included patients with a ppFEV₁ value between 40% and 90% of the predicted mean for age, sex, and height for those currently receiving ELX-TEZ-IVA, or a ppFEV₁ between 40% and 80% for those not currently receiving ELX-TEZ-IVA. In terms of CF-related genotype, patients recruited to the SKYLINE 102 trial had to be heterozygous for F508 del and a minimal function mutation, while patients recruited to the SKYLINE 103 trial had to have either homozygous F508del mutations, heterozygous F508del and a gating or residual function mutation, or at least 1 mutation identified as responsive to ELX-TEZ-IVA with no F508del mutation. All patients entered a 28-day run-in period receiving ELX-TEZ-IVA before being randomized 1:1 in a double-blind fashion to VNZ-TEZ-D-IVA or ELX-TEZ-IVA treatment for 52 weeks, followed by an additional 28-day open-label follow-up for additional safety data.

In the RIDGELINE study, patients aged between 1 and 11 years with a mutation responsive to ELX-TEZ-IVA were recruited. The RIDGELINE study included a part A, with the objective of evaluating the pharmacokinetics of VNZ, TEZ, D-IVA, and relevant metabolites when dosed in therapeutic concentrations, and evaluating the safety and tolerability of VNZ-TEZ-D-IVA. Part A preceded part B, and informed the doses and weight-related dose thresholds for part B, in which the objectives were primarily to evaluate the safety and tolerability of VNZ-TEZ-D-IVA through week 24, and secondarily to evaluate the efficacy through week 24 as well as the pharmacokinetics. Within parts A and B there were 3 cohorts each, divided

by age range, in which the first cohort included patients aged 6 to 11 years (inclusive), the second included patients aged 2 to 5 years (inclusive), and the third included patients aged 1 year to less than 2 years of age. Therefore, only cohort A1 (N = 17) and B1 (N = 78) are relevant to the Health Canada indication considered here, and only cohort B1 is associated with results data for efficacy outcomes considered in this review, although cohort A1 does also contribute to the safety data that will be assessed.

In the SKYLINE 102 trial, 59% of patients were male and 41% of patients were female, while in the SKYLINE 103 trial, 51% of patients were male and 49% were female. The mean age by treatment group in the RCTs at baseline was 31 to 34 years across the SKYLINE studies, and the treatment groups were similar for these categories in each study. In cohorts A1 and B1 in the RIDGELINE study, 58.8% and 56.4% of patients were male, 41.2% and 43.6% were female, and the mean age was 9.5 years and 9.3 years, respectively. The baseline patient characteristics for ppFEV₁ demonstrated more progressed disease in the studies that recruited older patients (aged 12 years or older, in the SKYLINE 102 and 103 trials) compared to cohorts A1 and B1 in the RIDGELINE study, which included patients aged 6 to 11 years; this reflects the natural course of CF, and there were no concerning within-study differences between treatment groups. In all studies, most patients had immediate prior experience with a *CFTR* modulator (84.6% to 94.1%), most commonly ELX-TEZ-IVA. The mean duration of prior ELX-TEZ-IVA use was approximately 2 years in the SKYLINE 102 and 103 RCTs, and approximately 1 year in cohort B1 of the RIDGELINE study. The SKYLINE 102 trial recruited patients who were heterozygous for F508del and a minimal function mutation; therefore, this genotype was represented in 100% of patients, while in the other studies the most common genotype was homozygous for F508del (47.4% to 78.2%). The majority of patients in every study were white (90.7% to 97.5%), while a smaller proportion were Black or African American (0% to 2.0%), Asian (0% to 0.5%), “other,” or not reported.

Efficacy Results

Number of Pulmonary Exacerbations

In the SKYLINE 102 trial (full analysis set [FAS]), the estimated event rate per year was 0.42 in the ELX-TEZ-IVA group (n = 50 with events) versus 0.32 in the VNZ-TEZ-D-IVA group (n = 60 with events). The pulmonary exacerbation rate difference was -0.10 events per year (95% confidence interval [CI], -0.24 to 0.04).

In the SKYLINE 103 trial (FAS), the annual event rate was 0.29 in the VNZ-TEZ-D-IVA group (n = 61 with events) and 0.26 in the ELX-TEZ-IVA group (n = 59 with events). The rate difference was 0.03 events per year (95% CI, -0.07 to 0.13).

In the RIDGELINE study, there were 6 patients in cohort B1 (FAS) who experienced an event, contributing to an annual event rate of 0.15.

No subgroup or sensitivity analyses were conducted for this end point in the included studies.

Time to First Pulmonary Exacerbation

In the SKYLINE 102 trial, based on a secondary analysis of the time to first pulmonary exacerbation during the analysis period in the FAS, the probability of event-free survival (Kaplan-Meier estimate) at 24 weeks was 0.820 (95% CI, 0.758 to 0.867) in the VNZ-TEZ-D-IVA group and 0.819 (95% CI, 0.758 to 0.866) in the

ELX-TEZ-IVA group, and at 52 weeks it was 0.741 (95% CI, 0.673 to 0.797) and 0.695 (95% CI, 0.626 to 0.755), respectively.

In the SKYLINE 103 trial, based on a secondary analysis of the time to first pulmonary exacerbation during the analysis period in the FAS, the probability of event-free survival (Kaplan-Meier estimate) at 24 weeks was 0.857 (95% CI, 0.810 to 0.893) in the VNZ-TEZ-D-IVA group and 0.882 (95% CI, 0.838 to 0.914) in the ELX-TEZ-IVA group, and at 52 weeks it was 0.783 (95% CI, 0.729 to 0.827) and 0.792 (95% CI, 0.739 to 0.835), respectively.

Time to first pulmonary exacerbation was not reported in the RIDGELINE study.

Pulmonary Exacerbations Requiring IV Antibiotics or Hospitalization

In the SKYLINE 102 trial (FAS), 10 patients (5.1%) in the VNZ-TEZ-D-IVA group and 26 patients (12.9%) in the ELX-TEZ-IVA group had pulmonary exacerbations requiring hospitalization or IV antibiotic therapy during the analysis period. The probability of event-free survival at 24 weeks (Kaplan-Meier estimate) was 0.969 (95% CI, 0.933 to 0.986) in the VNZ-TEZ-D-IVA group and 0.935 (95% CI, 0.890 to 0.962) in the ELX-TEZ-IVA group, and at 52 weeks was 0.948 (95% CI, 0.906 to 0.972) in the VNZ-TEZ-D-IVA group and 0.868 (95% CI, 0.813 to 0.908) in the ELX-TEZ-IVA group. Of these patients with events, all required IV antibiotic therapy. In addition to the IV antibiotic therapy, 8 patients in the VNZ-TEZ-D-IVA group and 17 patients in the ELX-TEZ-IVA group required hospitalization.

In the SKYLINE 103 trial (FAS), 19 patients (6.7%) in the VNZ-TEZ-D-IVA group and 17 patients (5.9%) in the ELX-TEZ-IVA group had pulmonary exacerbations requiring hospitalization or IV antibiotic therapy. The probability of event-free survival at 24 weeks (Kaplan-Meier estimate) was 0.961 (95% CI, 0.930 to 0.978) in the VNZ-TEZ-D-IVA group and 0.962 (95% CI, 0.932 to 0.979) in the ELX-TEZ-IVA group, and at 52 weeks it was 0.931 (95% CI, 0.894 to 0.956) in the VNZ-TEZ-D-IVA group and 0.940 (95% CI, 0.906 to 0.962) in the ELX-TEZ-IVA group. Of these patients, all required IV antibiotic therapy, and 14 of the patients in the VNZ-TEZ-D-IVA group and 9 of the patients in the ELX-TEZ-IVA group additionally required hospitalization.

In cohort B1 of the RIDGELINE study, 1 patient required both hospitalization and IV antibiotic therapy (1.3%), for an observed event rate per year of 0.03.

Percent Predicted Forced Expiratory Volume in 1 Second The primary outcome of ppFEV₁ was evaluated in the FAS through week 24 in the SKYLINE 102 trial (n = 196 in the VNZ-TEZ-D-IVA group and n = 202 in the ELX-TEZ-IVA group) and SKYLINE 103 trial (n = 284 and n = 289, respectively). In the mixed model for repeated measures (MMRM) analysis of noninferiority comparing VNZ-TEZ-D-IVA to ELX-TEZ-IVA, the least squares (LS) mean treatment difference was 0.2% (1-sided P < 0.0001; 95% CI, -0.7% to 1.1%) in the SKYLINE 102 trial and 0.2% (1-sided P for noninferiority < 0.0001; 95% CI, -0.5% to 0.9%) in the SKYLINE 103 trial. The prespecified noninferiority margin was -3.0%; therefore, the results of both studies met the preplanned primary analysis of noninferiority for ppFEV₁ as neither 95% CI crossed the noninferiority margin.

In cohort B1 of the RIDGELINE study (n = 78), patients treated with VNZ-TEZ-D-IVA showed similar ppFEV₁ values compared to baseline use of ELX-TEZ-IVA, based on a within-group LS mean absolute change from baseline to 24 weeks of 0% (95% CI, -2.0% to 1.9%).

The secondary end point of ppFEV₁ through 52 weeks showed similar results in both studies, consistent with the 24-week primary analyses. In the SKYLINE 102 trial, the LS mean difference in absolute change from baseline was 0.1% (95% CI, -0.8% to 1.0%). In the SKYLINE 103 trial, it was 0.3% (95% CI, -0.4% to 1.0%).

In the SKYLINE 102 and SKYLINE 103 trials, a supplementary sensitivity analysis was conducted using an alternative estimand where intercurrent events were addressed using the hypothetical strategy for the 24-week outcome of ppFEV₁, and the results were consistent with the primary analyses.

Subgroup analyses were conducted on the primary outcome at 24 weeks in the SKYLINE 102 and SKYLINE 103 trials based on age (younger than 18 years versus at least 18 years at screening) and ppFEV₁ at baseline (less than 70% versus at least 70%). Most of the results fell within the noninferiority margin of -3.0% and were similar to the primary analysis results. However, in the SKYLINE 102 trial, in the subgroup of patients younger than 18 years at screening, the 95% CI crossed this threshold (LS mean difference = -1.3%; 95% CI, -3.9% to 1.3%). In the SKYLINE 103 trial, the value for this subgroup was 0.9% (95% CI, -1.2% to 3.0%).

No subgroup or sensitivity analyses were conducted in the RIDGELINE study or for the week 52 outcomes in the SKYLINE studies.

Body Mass Index

In the RIDGELINE study, the absolute change in BMI at week 24 was an LS mean of 0.22 kg/m² (95% CI, 0.05 kg/m² to 0.38 kg/m²).

In the SKYLINE 102 trial, the LS mean change from baseline in BMI in the VNZ-TEZ-D-IVA group (n = 179) and ELX-TEZ-IVA group (n = 187) at week 52 was 0.30 kg/m² (standard error [SE] = 0.10 kg/m²) and 0.08 kg/m² (SE = 0.10 kg/m²), respectively, with an LS mean difference of 0.22 kg/m² (95% CI, -0.05 kg/m² to 0.49 kg/m²).

In the SKYLINE 103 trial, the LS mean change from baseline in BMI in the VNZ-TEZ-D-IVA group (n = 248) and ELX-TEZ-IVA group (n = 266) at week 52 was 0.37 kg/m² (SE = 0.08 kg/m²) and 0.22 kg/m² (SE = 0.07 kg/m²), respectively, with an LS mean difference of 0.16 kg/m² (95% CI, -0.05 kg/m² to 0.36 kg/m²).

No subgroup or sensitivity analyses were reported.

BMI Z Score

In the RIDGELINE study, the absolute change in BMI z score at week 24 was an LS mean of -0.05 (SE = 0.03; 95% CI, -0.12 to 0.02).

In the SKYLINE 102 trial, at 52 weeks, the LS mean change from baseline in BMI z score among patients aged 20 years or younger at baseline was 0.25 (SE = 0.10) in the VNZ-TEZ-D-IVA group (n = 27) and -0.09 (SE = 0.09) in the ELX-TEZ-IVA group (n = 32), with an LS mean difference of 0.34 (95% CI, 0.07 to 0.61).

In the SKYLINE 103 trial, the LS mean change from baseline in BMI z score among patients aged 20 years or younger at baseline was 0.11 (SE = 0.06) in the VNZ–TEZ–D-IVA group (n = 42) and –0.13 (SE = 0.07) in the ELX-TEZ-IVA group (n = 35), with an LS mean difference of 0.24 (95% CI, 0.06 to 0.42) at 52 weeks.

No subgroup or sensitivity analyses were reported.

CFQ-R Respiratory Domain

HRQoL was measured using the CFQ-R Respiratory domain.

In the SKYLINE 102 trial, the LS mean change in CFQ-R Respiratory domain score through week 24 was 0.5 points (SE = 1.1) in the VNZ–TEZ–D-IVA group (n = 186) and –1.7 points (SE = 1.0) in the ELX-TEZ-IVA group (n = 192). The LS mean difference was 2.3 points (95% CI, –0.6 to 5.2).

In the SKYLINE 103 trial, the LS mean change from baseline in CFQ-R Respiratory domain score was –1.2 points (SE = 0.8) in the VNZ–TEZ–D-IVA group (n = 268) and –1.2 points (SE = 0.8) in the ELX-TEZ-IVA group (n = 270) as well. The LS mean difference was –0.1 points (95% CI, –2.3 to 2.1).

Patients treated with VNZ–TEZ–D-IVA in cohort B1 of the RIDGELINE study had a within-group LS mean absolute change from baseline through week 24 of 3.9 points (95% CI, 1.5 to 6.3).

Through week 52, the LS mean change in the SKYLINE 103 trial in the VNZ–TEZ–D-IVA group (n = 186) and ELX-TEZ-IVA group (n = 192) was 0.8 points (SE = 1.0) and –1.6 points (SE = 1.0), respectively, with an LS mean difference of 2.4 points (95% CI, –0.3 to 5.1).

In the SKYLINE 103 trial, the LS mean change in the VNZ–TEZ–D-IVA group (n = 268) and ELX-TEZ-IVA group (n = 270) through 52 weeks was –0.4 points (SE = 0.7) and –1.0 points (SE = 0.7), respectively, with an LS mean difference of 0.7 points (95% CI, –1.4 to 2.7).

No subgroup or sensitivity analyses were reported.

Sweat Chloride

In SKYLINE 102, the LS mean absolute change from baseline for SwCl through week 24 (FAS) was –7.5 mmol/L (standard deviation [SD] = 0.8) in the VNZ–TEZ–D-IVA group (n = 196) compared to 0.9 mmol/L (SD = 0.8) in the ELX-TEZ-IVA group (n = 202). The MMRM analysis of this secondary end point reported a reduction (i.e., improvement) in SwCl associated with VNZ–TEZ–D-IVA treatment compared to ELX-TEZ-IVA treatment (LS mean difference = –8.4 mmol/L; 95% CI, –10.5 to –6.3 mmol/L; P < 0.0001).

In the SKYLINE 103 trial, the LS mean absolute change from baseline in SwCl through week 24 (FAS) was –5.1 mmol/L (SD = 0.7) in the VNZ–TEZ–D-IVA group (n = 294) compared to –2.3 mmol/L (SD = 0.7) in the ELX-TEZ-IVA group (n = 289). The MMRM analysis reported a reduction (i.e., improvement) in SwCl associated with VNZ–TEZ–D-IVA treatment compared to ELX-TEZ-IVA treatment (LS mean difference = –2.8 mmol/L; 95% CI, –4.7 to –0.9 mmol/L; P = 0.0034).

In the single-arm RIDGELINE study, the within-group LS mean absolute change from baseline through week 24 (averaging weeks 16 and 24) was –8.6 mmol/L (95% CI, –11.0 mmol/L to –6.3 mmol/L) in the cohort B1 FAS (n = 77).

In the SKYLINE 102 trial, the LS mean absolute change from baseline in SwCI through week 52 (FAS) was -7.5 mmol/L (SD = 0.7) in the VNZ–TEZ–D-IVA group (n = 196) compared to 0.5 mmol/L (SD = 0.7) in the ELX-TEZ-IVA group (n = 202). The MMRM analysis reported a reduction (i.e., improvement) in SwCI associated with VNZ–TEZ–D-IVA treatment, with an LS mean difference of -8.0 mmol/L (95% CI, -9.9 mmol/L to -6.1 mmol/L).

In the SKYLINE 103 trial, the LS mean change in the VNZ–TEZ–D-IVA group (n = 284) was -5.0 mmol/L (SD = 0.6) and in the ELX-TEZ-IVA group it was -2.2 mmol/L (SD = 0.6). The MMRM analysis reported a reduction (i.e., improvement) in SwCI associated with VNZ–TEZ–D-IVA treatment, with an LS mean difference of -2.8 mmol/L (95% CI, -4.6 mmol/L to -1.0 mmol/L).

No subgroup or sensitivity analyses were reported.

Proportion of Patients With SwCI of 30 mmol/L or Lower

The 24-week pooled outcome including data from both the SKYLINE 102 and SKYLINE 103 trials reported an odds ratio of 2.87 (95% CI, 2.00 to 4.12; $P < 0.0001$), indicating patients treated with VNZ–TEZ–D-IVA were more likely to have a SwCI of 30 mmol/L or lower at week 24 than patients treated with ELX-TEZ-IVA.

In the RIDGELINE study, 41 out of 78 patients (52.6%) had a SwCI of 30 mmol/L or lower at week 24 (95% CI, 40.9% to 64.0%).

The 52-week result in the SKYLINE 102 trial was an odds ratio of 5.77 (95% CI, 3.33 to 9.99) and in the SKYLINE 103 trial was an odds ratio of 1.98 (95% CI, 1.36 to 2.88). While the magnitude of difference between the treatment arms appeared to vary between the 2 studies, the trend was in the same direction and aligned with the 24-week outcome reported in these studies.

No subgroup or sensitivity analyses were reported.

Harms Results

To contextualize the safety data from both the SKYLINE 102 and SKYLINE 103 trials, it is important to note that the majority of patients received commercial ELX-TEZ-IVA before study enrolment, with a median exposure of approximately 2 years, and all patients received ELX-TEZ-IVA for 4 weeks during the run-in period. Additionally, patients who had a prior history of intolerance to ELX-TEZ-IVA were not eligible to enrol, and patients who developed intolerance to ELX-TEZ-IVA during the run-in period were discontinued from the study. Therefore, the safety data from the ELX-TEZ-IVA group are reflective of the experience in patients who have tolerated ELX-TEZ-IVA and who have continued with an existing treatment regimen, and the safety data from the VNZ–TEZ–D-IVA group are reflective of patients who initiated a new treatment regimen.

Similarly, in the RIDGELINE study, all patients either had prior experience taking ELX-TEZ-IVA or participated in a run-in period in which they received ELX-TEZ-IVA, and then switched to VNZ–TEZ–D-IVA during the study period.

Overall AEs

In the SKYLINE 102 and SKYLINE 103 trials, 94.4% and 96.5% of patients treated with VNZ–TEZ–D-IVA experienced any AE, while 97% and 94.5% of patients treated with ELX-TEZ-IVA experienced any AE. In both studies, the most common AEs were infective pulmonary exacerbations related to CF (26.8% to 34.7% across the treatment groups in both studies), COVID-19 (20.4% to 26.7%), cough (20.3% to 23.0%), and nasopharyngitis (17.3% to 23.0%).

In the RIDGELINE study, the proportion of patients with at least 1 AE was 70.6% in cohort A1 and 96.2% in cohort B1.

Serious AEs

In the SKYLINE 102 and SKYLINE 103 trials, among patients treated with VNZ–TEZ–D-IVA, 14.3% and 14.1% experienced any SAE, while 20.3% and 13.8% treated with ELX-TEZ-IVA experienced any SAE. In the SKYLINE 102 trial, the proportion of patients with any SAE appeared elevated in the ELX-TEZ-IVA group relative to the VNZ–TEZ–D-IVA group, but this was not the case in the SKYLINE 103 trial, in which the values were similar across the 2 treatment groups. One life-threatening AE occurred, which was an infective pulmonary exacerbation of CF in a patient in the ELX-TEZ-IVA treatment group in the SKYLINE 103 trial.

In the 2 RCTs, the most common SAE was infective pulmonary exacerbation of CF. In the SKYLINE 102 trial, this occurred in 5.6% of patients treated with VNZ–TEZ–D-IVA, and 11.4% of patients treated with ELX-TEZ-IVA. In the SKYLINE 103 trial, this occurred in 6.3% and 4.2%, respectively. Other SAEs were individually uncommon (0% to approximately 2% of patients for each SAE) but included influenza, hemoptysis, pneumonia, suicidal ideation, syncope, COVID-19, increased alanine aminotransferase, increased ALT or AST, constipation, distal intestinal obstruction syndrome, increased gamma-glutamyl transferase, cholelithiasis, and nephrolithiasis.

In the RIDGELINE study, no patients in cohort A1 had any SAEs, and 6 patients (7.7%) in cohort B1 had any SAE. In cohort B1, the SAEs included infective pulmonary exacerbations ($n = 2$). Other SAEs occurring in 1 patient (1.3%) each were failure to thrive, adenovirus infection, constipation, decreased pulmonary function test, and cough. No life-threatening AEs occurred.

Withdrawals Due to AEs

In the SKYLINE 102 trial, 2.0% of patients treated with VNZ–TEZ–D-IVA and 4.5% of patients treated with ELX-TEZ-IVA had an AE leading to treatment discontinuation. In the SKYLINE 103 trial, this occurred in 4.9% of those receiving VNZ–TEZ–D-IVA and 3.1% of those receiving ELX-TEZ-IVA. The AEs leading to treatment discontinuation were individually uncommon (0% to approximately 2% of patients for each AE) and included a variety of types of AEs.

In the RIDGELINE study, 1 patient (1.3%) had treatment interrupted due to a seizure and 1 patient stopped treatment due to AEs of fatigue and coughing. Both patients were in cohort B1.

Mortality

No deaths occurred in the SKYLINE 102 trial, SKYLINE 103 trial, or RIDGELINE study.

Notable Harms

Identified AEs of special interest included elevated transaminase levels, rash, elevated creatine kinase levels, cataracts, hypoglycemia, and neuropsychiatric events.

In the VNZ–TEZ–D-IVA and ELX-TEZ-IVA groups in the SKYLINE 102 trial, the proportions of patients with AEs of elevated transaminase levels were 8.2% and 6.4%, respectively; rash occurred in 8.7% and 7.4%; elevated creatinine occurred in 9.2% and 11.9%; hypoglycemia occurred in 2.6% and 3.5%; and neuropsychiatric AEs occurred in 8.7% and 13.9%. No patients in either treatment group had AEs of cataracts. No patients treated with VNZ–TEZ–D-IVA had serious elevated transaminase levels, rash, creatine kinase elevation, cataracts, or hypoglycemia events. Serious neuropsychiatric events occurred in 3 patients (1.5%) treated with VNZ–TEZ–D-IVA and in 2 patients (1.0%) treated with ELX-TEZ-IVA.

In the VNZ–TEZ–D-IVA and ELX-TEZ-IVA groups in the SKYLINE 103 trial, the proportions of patients with AEs of elevated transaminase levels were 9.5% and 7.6%, respectively; rash occurred in 12.7% and 8.0%; elevated creatine kinase levels occurred in 8.8% and 5.9%; cataracts occurred in [REDACTED] hypoglycemia occurred in 1.1% and 3.8%; and neuropsychiatric AEs occurred in 13.4% and 10.7%. Serious neuropsychiatric events occurred in 1 patient (0.4%) treated with VNZ–TEZ–D-IVA and 2 patients (0.7%) treated with ELX-TEZ-IVA. Serious elevated transaminase events occurred in [REDACTED] patients treated with VNZ–TEZ–D-IVA and [REDACTED] in the ELX-TEZ-IVA group. Events of serious creatine kinase elevation occurred in 1 patient (0.4%) in the VNZ–TEZ–D-IVA group and none in the ELX-TEZ-IVA group. No patients had serious rash, cataracts, or hypoglycemia events.

In cohort A1 of the RIDGELINE study, there were no events of increased ALT, increased AST, elevated creatine kinase levels, cataracts, hypoglycemia, or neuropsychiatric AEs, while 3 patients (17.6%) had rash. In cohort B1, ALT increase occurred in 5.1% of patients, AST increase in 2.6%, rash in 5.1%, elevated creatine kinase levels in 2.6%, cataracts in 1.3%, and neuropsychiatric events in 5.1%; no patients in cohort B1 had hypoglycemia. No patients in either cohort had serious elevated transaminase levels, rash, creatine kinase elevation, cataracts, hypoglycemia, or neuropsychiatric events.

Critical Appraisal

The SKYLINE 102 and SKYLINE 103 trials were double-blind, parallel-group, randomized studies with appropriate randomization, allocation concealment, blinding, and methodological approaches. Patient disposition and baseline characteristics were well balanced between the study groups and there were relatively few major protocol violations or discontinuations of treatment or study. The primary end point of change in ppFEV₁ at 24 weeks was a formal noninferiority assessment tested at a 1-sided alpha level of 0.025, which was met according to the prespecified noninferiority margin of –3%. This margin is consistent with the statistical approach selected and has been used in previous studies of CF.^{7,8} It was considered to be appropriate by the clinical experts consulted by CDA-AMC, who noted that a between-group difference of approximately 5% in ppFEV₁ may be the minimum clinically significant difference, although there is no published consensus. Other outcomes were assessed using two-sided alpha levels of 0.05. All missing data were assumed to be missing at random and were not imputed, and there was a generally low proportion of patients (less than 10%) with missing data that was well balanced between the treatment groups for each

end point as of the 52-week outcomes in both studies. Given the expected similarity in the treatment efficacy and safety profiles, this aligned with expectations, albeit there was a slight imbalance in discontinuations due to AEs in SKYLINE 102. The 52-week end points assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach were not included in the hierarchical testing procedure and were not adjusted for multiplicity. This may raise the risk of bias but was not considered to be particularly significant in the context of these noninferiority studies.

The RIDGELINE study was a single-arm, noncomparative, nonrandomized, open-label study that assessed similar outcomes to the SKYLINE 102 and 103 studies in terms of within-group change from baseline after 24 weeks of therapy with VNZ–TEZ–D-IVA. Because this was a noncomparative, nonrandomized study, the risk of bias is high and the degree of certainty in the results with comparison to ELX-TEZ-IVA is very low. This is especially the case for the self-reported HRQoL metric of the CFQ-R Respiratory domain.

The SKYLINE 102 and SKYLINE 103 trials reflect the patient population aged 12 years and older with CF, while cohorts A1 and B1 of the RIDGELINE study recruited patients aged 6 to 11 years, inclusive. The eligibility criteria and baseline characteristics were considered appropriate and reflective of the patient population with CF in Canada within those age groups, and were considered appropriate and reflective of the patients expected to be eligible for treatment with VNZ–TEZ–D-IVA. The comparator, treatment setting, concomitant medications, and patient eligibility criteria were relevant and generalizable to the Canadian treatment setting. Because all of the included patients had treatment experience with ELX-TEZ-IVA and/or participated in run-in periods with ELX-TEZ-IVA treatment, and patients intolerant to or ineligible for ELX-TEZ-IVA were not included, the efficacy and safety data during the treatment period of the studies reflects the experience of patients switching from 1 *CFTR* modulator to another (if assigned VNZ–TEZ–D-IVA), or reflects the experience of patients continuing on a therapy that they have demonstrated tolerance to (if assigned to ELX-TEZ-IVA in the RCTs). This represents a gap in the generalizability of these studies, as patients naive to *CFTR* modulator therapy beginning on VNZ–TEZ–D-IVA were not captured. However, this is expected to be a minority of patients.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- number of pulmonary exacerbations per year
- change from baseline to 52 weeks in:
 - lung function as measured by ppFEV₁
 - BMI
 - BMI z score in pediatric patients
 - HRQoL as measured by CFQ-R Respiratory domain score
 - SwCI
- safety outcomes:

- number of patients with AEs of elevated transaminases
- number of patients with SAEs.

Results of GRADE Assessments

[Table 4](#) presents the GRADE summary of findings for VNZ–TEZ–D-IVA versus ELX-TEZ-IVA for patients aged 12 years or older with CF. [Table 5](#) presents the GRADE summary of findings for VNZ–TEZ–D-IVA versus ELX-TEZ-IVA for patients aged 6 to 11 years with CF.

Table 4: Summary of Findings for VNZ–TEZ–D-IVA vs. ELX-TEZ-IVA for Patients Aged 12 Years or Older With CF

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Pulmonary exacerbations				
Number of pulmonary exacerbations, event rate per year Follow-up: 52 weeks	971 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D-IVA: 0.32 • ELX-TEZ-IVA: 0.42 • Rate difference (95% CI): –0.10 (–0.24 to 0.04) SKYLINE 103 trial: • VNZ–TEZ–D-IVA: 0.29 • ELX-TEZ-IVA: 0.26 • Rate difference (95% CI): 0.03 (–0.07 to 0.13)	Moderate ^a	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D-IVA likely results in little to no difference in the annual event rate of pulmonary exacerbations when compared with ELX-TEZ-IVA.
Lung function				
Change from baseline in ppFEV ₁ , LS mean percentage points (95% CI) Follow-up: 52 weeks	933 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D-IVA: 0.5 (–0.1 to 1.1) • ELX-TEZ-IVA: 0.4 (–0.3 to 1.0) • LS mean difference: 0.1 (–0.8 to 1.0) SKYLINE 103 trial: • VNZ–TEZ–D-IVA: 0.3 (–0.2 to 0.8) • ELX-TEZ-IVA: 0.0 (–0.5 to 0.5) • LS mean difference: 0.3 (–0.4 to 1.0)	High ^b	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D-IVA results in little to no difference (i.e., a noninferior effect) in the change in ppFEV ₁ when compared with ELX-TEZ-IVA.
Body weight				
Change from baseline in BMI, LS mean kg/m ² (95% CI) Follow-up: 52 weeks	880 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D-IVA: 0.30 (0.11 to 0.49) • ELX-TEZ-IVA: 0.08 (–0.11 to 0.27) • LS mean difference: 0.22 (–0.05 to 0.49)	Moderate ^c	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D-IVA likely results in little to no difference in the change in BMI when

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		SKYLINE 103 trial: • VNZ–TEZ–D–IVA: 0.37 (0.22 to 0.52) • ELX-TEZ-IVA: 0.22 (0.07 to 0.36) • LS mean difference: 0.16 (–0.05 to 0.36)		compared with ELX-TEZ-IVA.
Change from baseline in BMI z score among patients aged 20 years or younger, LS mean (95% CI) Follow-up: 52 weeks	136 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D–IVA: 0.25 (0.05 to 0.45) • ELX-TEZ-IVA: –0.09 (–0.27 to 0.09) • LS mean difference: 0.34 (0.07 to 0.61) SKYLINE 103 trial: • VNZ–TEZ–D–IVA: 0.11 (–0.01 to 0.23) • ELX-TEZ-IVA: –0.13 (–0.27 to 0.01) • LS mean difference: 0.24 (0.06 to 0.42)	Moderate ^d	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D–IVA likely results in little to no difference in the change in BMI z score when compared with ELX-TEZ-IVA.
Health-related quality of life				
Absolute change from baseline in CFQ-R Respiratory domain, LS mean points (95% CI) Follow-up: 52 weeks	916 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D–IVA: 0.8 (–1.1 to 2.7) • ELX-TEZ-IVA: –1.6 (–3.5 to 0.3) • LS mean difference: 2.4 (95% CI, –0.3 to 5.1) SKYLINE 103 trial: • VNZ–TEZ–D–IVA: –0.4 (–1.8 to 1.1) • ELX-TEZ-IVA: –1.0 (–2.5 to 0.4) • LS mean difference: 0.7 (–1.4 to 2.7)	Moderate ^e	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D–IVA likely results in little to no difference in the change in CFQ-R Respiratory domain score compared with ELX-TEZ-IVA.
Sweat Chloride				
Absolute change from baseline in SwCl, LS mean mmol/L (95% CI) Follow-up: 52 weeks	931 (2 RCTs)	SKYLINE 102 trial: • VNZ–TEZ–D–IVA: –7.5 (–8.9 to –6.2) • ELX-TEZ-IVA: 0.5 (–0.8 to 1.8) • LS mean difference: –8.0 (–9.9 to –6.1) SKYLINE 103 trial: • VNZ–TEZ–D–IVA: –5.0 (–6.2 to –3.7) • ELX-TEZ-IVA: –2.2 (–3.5 to –1.0)	Moderate ^f	Treatment of CF in patients aged 12 years or older with VNZ–TEZ–D–IVA likely reduces SwCl levels compared with ELX-TEZ-IVA. The clinical importance of a reduction in SwCl is unclear. Clinical experts judged the magnitude of the

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		LS mean difference: -2.8 (-4.6 to -0.9)		observed reduction to not be clinically meaningful. ^f
Harms				
Number of patients with elevated transaminase AEs, n (%) Follow-up: 52 weeks	981 (2 RCTs)	SKYLINE 102 trial: - VNZ-TEZ-D-IVA: 16 (8.2) - ELX-TEZ-IVA: 13 (6.4) - Difference: NR SKYLINE 103 trial: - VNZ-TEZ-D-IVA: 27 (9.5) - ELX-TEZ-IVA: 22 (7.6) - Difference: NR	Moderate ^g	Treatment of CF in patients aged 12 years or older with VNZ-TEZ-D-IVA likely results in little to no difference in the number of patients with AEs of elevated transaminases when compared with ELX-TEZ-IVA.
Number of patients with SAEs, n (%) Follow-up: 52 weeks	981 (2 RCTs)	SKYLINE 102 trial: - VNZ-TEZ-D-IVA: 28 (14.3) - ELX-TEZ-IVA: 41 (20.3) - Difference: NR SKYLINE 103 trial: - VNZ-TEZ-D-IVA: 40 (14.1) - ELX-TEZ-IVA: 40 (13.8) - Difference: NR	Moderate ^g	Treatment of CF in patients aged 12 years or older with VNZ-TEZ-D-IVA likely results in little to no difference in the number of patients with SAEs compared with ELX-TEZ-IVA.

AE = adverse event; BMI = body mass index; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; D-IVA = deutivacaftor; ELX = elexacaftor; IVA = ivacaftor; LS = least square; MID = minimal important difference; NR = not reported; ppFEV₁ = percent predicted forced expiratory volume in 1 second; RCT = randomized controlled trial; SAE = serious adverse event; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for imprecision due to the small number of events. Null was used as the threshold for potential benefit or harms in absence of a literature- or expert-informed MID, but this end point was not rated down an additional level because the narrow 95% CIs for the absolute between-group differences were judged by CDA-AMC to be unlikely to include important benefits or harms.

^bThe prespecified noninferiority margin for ppFEV₁ was 3%.

^cRated down 1 level for imprecision. The null was used as the threshold for potential benefit or harms in absence of a literature- or expert-informed MID. This efficacy outcome was also exploratory and not included in the primary or secondary estimand, increasing uncertainty in interpretation.

^dRated down 1 level for imprecision. The null was used as the threshold for potential benefit or harms in absence of a literature- or expert-informed MID. This efficacy outcome was also exploratory and not included in the primary or secondary estimand, increasing uncertainty in interpretation. Additionally, the sample size was small in this subgroup.

^eRated down 1 level for imprecision. The 95% CIs for the LS mean differences in both trials include values below the published MID threshold of 4 points for the CFQ-R Respiratory domain. Although both the point estimates are below the MID, the upper 95% CI of the SKYLINE 102 trial is greater than the MID, which was not observed in SKYLINE 103 trial. The outcome was only rated down 1 level as the observed effects are consistent with the hypothesis of noninferiority between the treatments and do not suggest meaningful difference in harm or benefit.

^fRated down 1 level for imprecision due to the lack of established MID. Notably, the clinical importance of further reduction in SwCl (beyond that seen with ELX-TEZ-IVA) is unclear, surrogacy of SwCl for clinical end points has not been established and was described by clinical experts to be unreliable, the magnitude of reduction in SwCl was not considered to be meaningful by clinicians as a patient may experience greater changes in SwCl day to day, and the reduction in SwCl observed in these studies does not appear to correlate with significant improvement in any other outcomes on this timescale. If further reduction in SwCl is clinically important, it may take much longer studies to elucidate this relationship.

^gRated down 1 level for imprecision. The null was used as the threshold for potential benefit or harms in absence of a literature- or expert-informed MID. Additionally, the small number of events increases uncertainty in the interpretation.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and the submitted Clinical Study Reports.

Table 5: Summary of Findings for VNZ-TEZ-D-IVA vs. ELX-TEZ-IVA for Patients Aged 6 to 11 Years With CF

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Pulmonary exacerbations				
Number of pulmonary exacerbations Follow-up: 24 weeks	78 (1 single-arm study)	RIDGELINE study cohort B1 • Number of events: 6 • Event rate per year: 0.15	Very low ^{a,b}	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on pulmonary exacerbation rate in patients with CF aged 6 to 11 years compared to any comparator.
Lung function				
Change from baseline in ppFEV ₁ , LS mean percentage points (95% CI) Follow-up: 24 weeks	74 (1 single-arm study)	RIDGELINE study cohort B1: • LS mean: 0.0 (−2.0 to 1.9)	Very low ^a	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on ppFEV ₁ in patients with CF aged 6 to 11 years compared to any comparator.
Body weight				
Change from baseline in BMI, LS mean kg/m ² (95% CI) Follow-up: 24 weeks	78 (1 single-arm study)	RIDGELINE study cohort B1: • LS mean: 0.22 (0.05 to 0.38)	Very low ^a	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on BMI in patients with CF aged 6 to 11 years compared to any comparator.
Change from baseline in BMI z score among patients aged 20 years or younger, LS mean (95% CI) Follow-up: 24 weeks	78 (1 single-arm study)	RIDGELINE study cohort B1: • LS mean: −0.05 (−0.12 to 0.02)	Very low ^a	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on BMI z score in patients with CF aged 6 to 11 years compared to any comparator.
Health-related quality of life				
Change from baseline in CFQ-R Respiratory domain, LS mean points (95% CI) Follow-up: 24 weeks	75 (1 single-arm study)	RIDGELINE study cohort B1: • LS mean: 3.9 (1.5 to 6.3)	Very low ^{a,c}	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on CFQ-R Respiratory domain score in patients with CF aged 6 to 11 years compared to any comparator.
Sweat Chloride				
Change from baseline in SwCl, LS mean mmol/L (95% CI) Follow-up: 24 weeks	75 (1 single-arm study)	RIDGELINE study cohort B1: • LS mean: −8.6 (−11.0 to −6.3)	Very low ^{a,d}	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on SwCl in patients with CF aged 6 to 11 years compared to any comparator.
Safety and tolerability				
Number of patients with elevated transaminase	112	RIDGELINE study: • Cohort A1: 0 (0%)	Very low ^{a,b}	The evidence is very uncertain about the effect of VNZ-TEZ-D-IVA on events of elevated

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
AEs, n (%) Follow-up: 24 weeks		• Cohort B1, elevated ALT: 4 (5.1%) • Cohort B1, elevated AST: 2 (2.6%)		transaminases in patients with CF aged 6 to 11 years compared to any comparator.
Number of patients with SAEs, n (%) Follow-up: 24 weeks	112	RIDGELINE study: • Cohort A1: 0 (0%) • Cohort B1: 6 (7.7%)	Very low ^{a,b}	The evidence is very uncertain about the effect of VNZ–TEZ–D-IVA on SAEs in patients with CF aged 6 to 11 years compared to any comparator.

AE = adverse event; BMI = body mass index; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; D-IVA = deutivacaftor; LS = least squares; MID = minimal important difference; NR = not reported; ppFEV₁ = percent predicted forced expiratory volume in 1 second; RCT = randomized controlled trial; SAE = serious adverse event; SwCl = sweat chloride; TEZ = tezacaftor; VNZ = vanzacaftor; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated as very low certainty due to serious concerns about study design and imprecision. The evidence is derived from a single-arm, noncomparative study, which limits the ability to attribute observed changes to the intervention and introduces a high risk of bias.

^bNo change from baseline was reported.

^cThe LS mean change from baseline was 3.9 points (95% CI, 1.5 to 6.3), just below the published MID target threshold of 4 points. Although the upper bound of the confidence interval exceeds the MID, the lack of a control group and the proximity of the point estimate to the threshold preclude rating up for magnitude of effect. Additionally, the CFQ-R is a self-reported outcome measure, which contributes to uncertainty and potential bias in the context of an unblinded, single-arm study.

^dThe clinical importance of further reduction in SwCl (beyond that seen with ELX-TEZ-IVA) is unclear, surrogacy of SwCl for clinical end points has not been established and was described by clinical experts to be unreliable, the magnitude of reduction in SwCl was not considered to be meaningful by clinicians as a patient may experience greater changes in SwCl day to day, and the reduction in SwCl observed in these studies does not appear to correlate with significant improvement in any other outcomes on this timescale. If further reduction in SwCl is clinically important, it may take much longer studies to elucidate this relationship.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and the submitted Clinical Study Report.

Long-Term Extension Studies

No long-term extension studies (with results) were submitted, although there are some presently ongoing for which results data are not yet available.

Indirect Comparisons

The sponsor submitted indirect comparisons between VNZ–TEZ–D-IVA and best supportive care; given the presence of direct evidence against ELX-TEZ-IVA, the standard of care, as previously discussed, this indirect comparison to supportive care was considered by CDA-AMC to have limited relevance, ergo it was not summarized or critically appraised for the purpose of this review.

Studies Addressing Gaps in the Evidence

Four nonclinical studies evaluating the effect of VNZ–TEZ–D-IVA on cells in an in vitro setting were provided. For *CFTR* mutations with low prevalence, a conventional clinical trial approach to demonstrate efficacy is not always feasible. To evaluate the potential clinical benefit of VNZ–TEZ–D-IVA in these circumstances, additional mutations were identified using the in vitro Fischer rat thyroid (FRT) system (with a threshold of 10% increase in chloride transport over baseline, as expressed as a percentage of normal), the in vitro human bronchial epithelial (HBE) primary cell culture model, and mechanistic data. There is precedent for using in vitro data in the approval of other *CFTR* modulator therapies (namely, ELX-TEZ-IVA) in Canada and

other countries. There were 303 *CFTR* mutations that were proposed by the sponsor to be responsive to VNZ–TEZ–D-IVA. Based on the Health Canada Notice of Compliance (NOC) for VNZ–TEZ–D-IVA issued on July 21, 2025, 266 *CFTR* gene mutations were approved as part of the indication, of which 23 were based on clinical data, 227 were based on in vitro data, and 16 were based on extrapolation. The remaining *CFTR* mutations that were submitted by the sponsor but not included in the Health Canada product monograph were excluded by Health Canada due to either of the following reasons: both the CFTR2 database and the CFTR-France database list them as *non-CF-causing*, or they are listed as *non-CF-causing* in 1 database and considered *variants of unknown significance* or only *CFTR-related disease-causing* in the other database and/or another source.

Economic Evidence

- VNZ–TEZ–D-IVA is available as tablets for oral administration (VNZ 4 mg, TEZ 20 mg, and D-IVA 50 mg; VNZ 10 mg, TEZ 50 mg, and D-IVA 125 mg). The sponsor has stated that VNZ–TEZ–D-IVA is dispensed as packages of 84 tablets of VNZ 4mg, TEZ 20mg, and D-IVA 50 mg or as packages of 56 tablets of VNZ 10 mg, TEZ 50 mg, and D-IVA 125 mg. The submitted price of both package sizes is \$24,696.00, which equates to a price of \$294.00 per VNZ 4 mg, TEZ 20 mg, and D-IVA 50 mg tablet and \$441.00 per VNZ 10 mg, TEZ 50 mg, and D-IVA 125 mg tablet. For both strengths, the annual cost of VNZ–TEZ–D-IVA is expected to be \$322,151 per patient, based on the Health Canada–recommended dosage.
- To inform the economic model, the sponsor used estimates of relative efficacy (change in ppFEV₁) for VNZ–TEZ–D-IVA and ELX-TEZ-IVA from the SKYLINE and RIDGELINE trials. The CDA-AMC Clinical Review found that, based on observations from the head-to-head noninferiority SKYLINE trial, VNZ–TEZ–D-IVA likely results in little to no difference in the annual rate of pulmonary exacerbations or change from baseline in ppFEV₁, compared with ELX-TEZ-IVA after 52 weeks of treatment among patients aged 12 years and older. Among patients aged 6 to 11 years, the evidence is very uncertain about the efficacy of VNZ–TEZ–D-IVA compared to any other treatment because of the single-arm design of the RIDGELINE trial. For pulmonary exacerbations, the sponsor used data from an indirect treatment comparison, the findings of which were inconsistent with the direct evidence submitted by the sponsor for pulmonary exacerbations. This indirect treatment comparison was not critically appraised by CDA-AMC due to the availability of head-to-head evidence.
- The results of the CDA-AMC base case suggest the following:
 - VNZ–TEZ–D-IVA is predicted to be associated with higher costs to the health care system than ELX-TEZ-IVA (incremental costs = \$494,835), primarily driven by increased costs associated with drug acquisition.
 - VNZ–TEZ–D-IVA is predicted to be associated with a gain of 0.07 life-years and a gain of 0.13 QALYs compared to ELX-TEZ-IVA.

- The incremental cost-effectiveness ratio of VNZ–TEZ–D-IVA compared to ELX-TEZ-IVA was \$3,727,216 per QALY gained in the CDA-AMC base case. More than 99% of the incremental QALYs were gained in the extrapolated period (i.e., after 52 weeks). In the absence of long-term data to support a difference in clinical outcomes, it is highly uncertain whether this difference will be realized in clinical practice. Additional price reductions than those presented in this report may therefore be required to achieve cost-effectiveness at a given willingness to pay threshold.

CDA-AMC estimates that the budget impact of reimbursing VNZ–TEZ–D-IVA for the indicated population will be approximately \$68 million over the first 3 years of reimbursement compared to the amount currently spent on ELX-TEZ-IVA, with an estimated expenditure of \$1 billion on VNZ–TEZ–D-IVA over this period. The actual budget impact of reimbursing VNZ–TEZ–D-IVA will depend on the uptake of VNZ–TEZ–D-IVA, the confidential price of ELX-TEZ-IVA, and the proportion of patients who have public drug plan coverage. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

Meeting date: September 24, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None



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