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CADTH Reimbursement Review

Patiromer (Veltassa)

Sponsor: Otsuka Canada Pharmaceutical Inc.

Therapeutic area: Hyperkalemia, adults (chronic kidney disease)

Clinical Review

Pharmacoeconomic Review

CADTH

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

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CPS	calcium polystyrene sulfonate
eGFR	estimated glomerular filtration rate
ED	emergency department
GI	gastrointestinal
ITT	intention to treat
LTMP	long-term maintenance period
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
RAASi	renin-angiotensin-aldosterone system inhibitor
SAE	serious adverse event
SD	standard deviation
SPS	sodium polystyrene sulfonate
T2DM	type 2 diabetes mellitus
TIP	treatment initiation period

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Potassium is an essential element in the human body that is tightly regulated by homeostatic mechanisms. Hyperkalemia refers to an elevated level of potassium in the plasma or serum, typically greater than 5.0 mmol/L, which is classified as mild (5.0 mmol/L to 5.9 mmol/L), moderate (6.0 mmol/L to 6.4 mmol/L), or severe (> 6.5 mmol/L).[1] Hyperkalemia is primarily caused by increased potassium release from the cells and reduced urinary potassium excretion, both of which may result from various clinical conditions (most commonly acute or chronic renal failure), or may be induced by medications (e.g., drugs that inhibit the renin-angiotensin-aldosterone system [RAASi]).[2] Patients who have impaired kidney function, such as those with chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, have an increased risk of hyperkalemia.[1] In Canada, it is estimated that the prevalence of CKD in primary care is 71.9 per 1,000 individuals, although CKD prevalence is increased among individuals with 3 or more other chronic diseases (281.7 per 1,000).[3] The exact incidence of hyperkalemia in the general population is unclear, since this is often a transient condition, although 1 Canadian study found only 2.6% of emergency department (ED) visits and 3.5% of hospital admissions were associated with hyperkalemia.[4]

Acute hyperkalemia can be an emergency event that requires immediate intervention and is usually treated with insulin, beta2-adrenergic agonists, bicarbonate, resins, fludrocortisone, aminophylline, and dialysis.[5] Chronic hyperkalemia requires ongoing management; patients with severe hyperkalemia require hospitalization and treatment with various IV therapies for rapid onset of action. Mild or moderate forms of hyperkalemia are generally treated with drugs that increase potassium excretion, such as oral loop or thiazide diuretics and cation-exchange resins or cation-exchange polymers.[6] This latter group of medications is known as potassium binders and have a delayed onset of action; examples include sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS), and patiromer.[6] Mild or moderate hyperkalemia can also be managed by limiting dietary intake of potassium and discontinuing or reducing the dose of medications that increase potassium, such as the RAASis.[4] Notably, while RAASi dose modification may help to normalize potassium levels, this can result in

Table 1: Submitted for Review

Item	Description
Drug product	Patiromer (Veltassa), 8.4 g, 16.8 g, 25.2 g patiromer (as patiromer sorbitex calcium), patiromer powder for oral suspension
Indication	For the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2)
Reimbursement request	For the treatment of hyperkalemia in patients with CKD 3 to 4 on RAASi therapy
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	October 3, 2018
Sponsor	Otsuka Canada Pharmaceutical

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NOC = Notice of Compliance; RAASi = renin-angiotensin-aldosterone system inhibitor.

patients losing the renal- and cardio-protective effects of these medications and, therefore, is not desired.[4]

Patiromer is a non-absorbed, potassium-binding, cation-exchange polymer that acts by reducing the concentration of free potassium in the gastrointestinal (GI) lumen, thereby reducing serum potassium levels. Health Canada initially granted patiromer a Notice of Compliance on October 3, 2018, which was revised on February 28, 2020, for the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2). The recommended starting dose of patiromer is 8.4 g once daily, which can be adjusted by 8.4 g in weekly intervals up to a maximum dose of 25.2 g once daily, based on the serum potassium level and the desired target range. Patiromer is available as a powder for oral suspension in 3 doses (8.4 g, 16.8 g, and 25.2 g), which should be suspended in a liquid before administration.[7]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of patiromer (as patiromer sorbitex calcium: 8.4 g, 16.8 g, and 25.2 g oral suspension) for the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2). Notably, the sponsor requested reimbursement for the treatment of hyperkalemia in patients with CKD stage 3 to 4 on RAASi therapy.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

One submission from the Kidney Foundation of Canada was received for this review. Information from 33 patients with CKD and caregivers was gathered from a survey using self-administered questionnaires. Respondents focused on the disease burden and treatment regimen for CKD, without much emphasis on hyperkalemia. CKD negatively impacts physical and/or mental health, the daily routine, and especially the career, of patients and caregivers. Patients indicated that early stages of CKD can be managed with medication, lifestyle changes, and a reduction of dietary sodium and potassium intake. A number of patients who had experience with SPS, CPS, and patiromer treatment were unsatisfied with the texture, frequency, and taste of SPS and CPS. In advanced stages, such as kidney failure, dialysis and kidney transplant become the only option, which heavily restricts day-to-day life and requires patients to limit potassium intake to avoid hyperkalemia between treatments. Survey respondents expected new CKD therapies to be affordable, effective, and associated with minimal side effects, have convenient administration (e.g., frequency and ease), facilitate life with CKD with ease, and provide a good quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

One clinical expert, with expertise in kidney disease, provided input for this review. The clinical expert indicated that hyperkalemia is at least initially treated by withdrawing medications that increase potassium, in particular, RAASis and mineralocorticoid receptor antagonists (MRAs). This approach, however, means that patients will lose the cardio- and renal-protective effects of RAASi and be at higher risk for adverse clinical outcomes. Other treatments for chronic hyperkalemia include potassium binders such as SPS, diuretics, or laxatives. All treatments include dietary counselling to modify foods that are high in potassium. The goal

of treatment is to prevent life-threatening arrhythmias and enable optimal dosing of an RAASi. Patiromer would be considered as adjunctive treatment primarily in patients who experience hyperkalemia while on an RAASi. As hyperkalemia is usually asymptomatic, blood testing of serum potassium is needed to identify patients in need of treatment and to monitor afterward. Patients with serum potassium of less than 5.5 mmol/L are least suitable for treatment. While serum potassium is the immediate, surrogate outcome to monitor hyperkalemia, the most important outcome from a clinical perspective is a reduction in the risk of cardiovascular or kidney disease outcomes by continuing optimal doses of an RAASi. Patiromer should be prescribed in community or hospital-based specialty clinics by specialists in cardiology, nephrology, endocrinology, or general internal medicine.

Clinician Group Input

This is input received from clinician groups, not the clinical expert consulted by CADTH throughout the review.

The input was provided by 1 individual clinician at Sunnybrook Hospital and 1 input on behalf of 10 clinicians at the Scarborough Regional Nephrology Program. Both clinician inputs were received from clinicians practising in Ontario.

The clinicians noted the treatment goal with patiromer is for the treatment of hyperkalemia to optimize medical therapy for cardiac conditions, potentially reducing mortality, and to decrease hospitalizations and ED visits.

The clinicians noted that patiromer has a place in therapy for hyperkalemia, specifically for cardiac and renal patients. The clinicians also noted that all patients seem to respond to treatment with potassium binders and patients who are most in need are those with acute hyperkalemia who would otherwise spend unnecessary time in the ED. Additionally, clinicians noted that patients with chronic disease, who cannot be on an appropriate dose of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or MRAs due to hyperkalemia, would benefit the most.

Drug Program Input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation.

Clinical factors:

- The definition of hyperkalemia and the threshold of serum potassium at which clinicians would initiate treatment with patiromer.
- The place in therapy of patiromer relative to currently available treatments for hyperkalemia.
- The expected duration of treatment with patiromer.

The clinical experts consulted by CADTH weighed evidence from the OPAL-HK trial and other clinical considerations to provide responses, which can be found in the Drug Program Input section.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One phase III trial, OPAL-HK (RLY5016-301),[8] was included in this review. OPAL-HK was a 2-part, single-blind (patient-blinded) study designed to assess the safety and efficacy of patiromer in patients with hyperkalemia (serum potassium of between 5.1 mmol/L and 6.5 mmol/L) and CKD (eGFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2) who were receiving a stable dose of at least 1 RAASi. The study had 2 sequential parts: Part A was designed to evaluate the efficacy of patiromer in correcting (reducing) serum potassium in hyperkalemic patients; part B was designed to assess maintenance of control of serum potassium. Part A was a 4-week non-randomized treatment phase during which 243 patients were assigned to a starting patiromer dose of 8.4 g/day (dose group 1, n = 92) or 16.8 g/day (dose group 2, n = 151), if their screening serum potassium was 5.1 mmol/L to less than 5.5 mmol/L, or greater than 5.5 mmol/L to less than 6.5 mmol/L, respectively. Part B was an 8-week, stratified, randomized, placebo-controlled, parallel-group, withdrawal phase, during which 107 patients who responded to part A treatment (achieved serum potassium within 3.8 mmol/L and < 5.1 mmol/L) and had a part A baseline serum potassium of 5.5 mmol/L or greater (maximum < 6.5 mmol/L) were randomized (1:1) to receive placebo at a fixed dose of 8 g/day (n = 52) of patiromer at their regular dose (n = 55). The patiromer dose was adjusted throughout the study (from 0 g/day to 50.4 g/day) to maintain serum potassium within a target range (3.8 mmol/L to 5.5 mmol/L). RAASi dose was generally adjusted (dose reduced or discontinued) only during part B to maintain serum potassium levels of less than 5.5 mmol/L. At the end of each part, patients who completed or discontinued that part entered a follow-up period for up to 2 weeks, during which they did not receive any study treatment and had their serum potassium monitored.

The primary efficacy end point was the change in serum potassium from the respective baseline to week 4 of each part of the study. Secondary end points included the proportion of patients with serum potassium within 3.8 mmol/L to less than 5.1 mmol/L at week 4 (part A), and 5.1 mmol/L or greater, or 5.5 mmol/L or greater at week 8 (part B). Exploratory efficacy outcomes evaluated concomitant RAASi dosing and patiromer dose adjustments.

Baseline characteristics were largely similar between groups in part A and B, respectively. Patients were mostly White males aged 65 years; more than 90% had CKD stage 3 to 4 (or higher) and hypertension, and approximately 40% to 60% of patients had heart failure and type 2 diabetes mellitus (T2DM). All patients were on an RAASi, as required by the study inclusion criteria; approximately 80% and 50% of participating patients received non-RAASi non-diuretic antihypertensives, and non-RAASi diuretics, respectively.

Efficacy Results

All efficacy results were reported in the intention-to-treat (ITT) population of the respective parts. Results on serum potassium were based on central laboratory measurements. For both parts, change in serum potassium was measured from baseline of the respective parts.

Part A

The primary efficacy outcome, i.e., the mean change from baseline in serum potassium (standard deviation [SD]) at week 4 in dose group 1 and 2 (screening serum potassium 5.1 mmol/L to < 5.5 mmol/L or ≥ 5.5 mmol/L to < 6.5 mmol/L, respectively), were −0.65 mmol/L (0.049 mmol/L) and −1.23 mmol/L (0.04 mmol/L), respectively. For the combined dose

groups, there was a statistically significant mean change of −1.01 mmol/L (0.03 mmol/L) in serum potassium from part A baseline through week 4 (P < 0.001). The primary efficacy end point met the threshold value for serum potassium change from baseline set by the FDA to be considered clinically important (≥ 0.7 mmol/L, with P < 0.05). Subgroup analyses showed baseline serum potassium was the only factor that affected the level of change in serum potassium from baseline, with higher baseline values associated with larger mean changes in potassium, as expected.

The secondary end point, i.e., the proportion of patients with a serum potassium level within the target range (≥ 3.8 mmol/L to < 5.1 mmol/L) at week 4 was 76% (95% confidence interval [CI], 70% to 81%) overall (both dose groups), with similar percentages in each dose group (74% and 77% in dose group 1 and 2, respectively). Results were stratified by heart failure, T2DM, and the part A baseline serum potassium value (< 5.5 mmol/L or ≥ 5.5 mmol/L).

Part B

Among the 107 patients at part B baseline, both the placebo and patiromer groups had a similar distribution of serum potassium, 4.45 mmol/L and 4.49 mmol/L, respectively. At the end of week 4, patients in the placebo group had a median increase of 0.72 mmol/L in serum potassium; the patiromer group had 0.00 median change. The estimated between-group difference in median change was statistically significant (0.72 mmol/L; P < 0.001). Subgroup analysis showed a similar direction of effects across all relevant subgroups (T2DM, heart failure, part A baseline serum potassium level, maximal RAASi medication).

The secondary end points for part B were the proportions of patients with a serum potassium of 5.1 mmol/L or greater and 5.5 mmol/L or greater at any point post-baseline through week 8. A statistically significantly greater proportion of patients in the placebo group had a serum potassium outside of the target range compared with patiromer: 91% versus 43% for 5.1 mmol/L or greater and 60% versus 15% for 5.5 mmol/L or greater (P < 0.001 for both). Notably, a Hochberg correction was used in assessing these 2 end points to ensure an overall type I error rate of 0.05. The objective for part B of the study was therefore met: patiromer resulted in a continuous management of serum potassium and prevented the recurrence of hyperkalemia, whereas treatment with placebo after withdrawing from patiromer resulted in an overall increase in serum potassium.

Exploratory analyses on dose adjustment showed 73% of patients on patiromer did not require additional modification of RAASi or patiromer doses for recurrent hyperkalemia to complete part B, compared with 33% of patients on placebo. In the placebo group, 66% and 56% of patients had a reduction in RAASi dose or complete discontinuation of RAASi medications because of hyperkalemia, respectively. In contrast, 6% of patients in the patiromer group had a reduction or discontinuation of RAASi medications because of hyperkalemia. By the end of part B, more patiromer-treated patients (94%) were still receiving an RAASi medication than patients given placebo (44%).

Harms Results

In part A, a similar percentage of patients in both dose groups (46% and 48% in dose group 1 and 2, respectively) experienced adverse events (AEs). The most commonly reported AEs included GI disorders and metabolism and nutrition disorders, with constipation reported for more than 5% of patients in both groups. During part B, 50% and 47% patients in the placebo and patiromer group experienced AEs, respectively.

A total of 4 patients had serious adverse events (SAEs) throughout the study. Seventeen patients withdrew from the study due to AEs, and 1 person died due to mesenteric vessel thrombosis.

Among the notable harms identified in the review protocol, constipation was reported for 11% and 4% patients in part A and B, respectively, while diarrhea, hypomagnesemia, and hypokalemia were reported by less than 5% of patients in either part, regardless of treatment. Due to the short duration of the trial (12 weeks), important safety signals may not have been captured. Health Canada's assessment of pooled data, including data from 4 phase II and III trials, with durations ranging from 28 days to 1 year, did not identify new or major safety signals beyond what was reported in OPAL-HK.

Critical Appraisal

The OPAL-HK trial had several internal and external validity issues unique to part A and part B. In part A, 10% of patients did not complete part A, and 8% had major protocol violations.

Table 2: Summary of Key Efficacy Results — OPAL-HK Part A (mITT Population)

Key efficacy results	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 90	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 147	Total 5.1 mmol/L to < 6.5 mmol/L N = 237
Primary efficacy end point, change in serum potassium, mmol/L			
Part A baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Part A week 4[a]			
Mean change ± SE	−0.65 ± 0.049	−1.23 ± 0.040	−1.01 ± 0.031
95% CI	−0.74 to −0.55	−1.31 to −1.16	−1.07 to −0.95
P value[b]	NA	NA	< 0.001
Secondary efficacy end point, proportion of patients with serum potassium in the target range (3.8 mmol/L to < 5.1 mmol/L) at week 4			
Stratified percentage, % (95% CI)[c]			
Success	74 (65 to 82)	77 (70 to 83)	76 (70 to 81)
Failure: Either reason[d]	26 (18 to 35)	23 (17 to 30)	24 (19 to 30)

CI = confidence interval; ITT = intention to treat; mITT = modified intention to treat; NA = not applicable; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation; SE = standard error.

Note: The mITT population consisted of 237 out of the 243 patients in the ITT population. Patients enrolled into the part A treatment phase received at least 1 dose of patiromer and had either a central or local laboratory serum potassium result at part A baseline, and at least 1 post-baseline weekly visit (i.e., part A week 1 or later). Six of the 243 patients in the ITT set had no post-baseline serum potassium because of early withdrawal from part A.

[a]The estimates for part A week 1 through part A week 4 come from a longitudinal model with: weekly post-baseline measurements from part A as the response variables, 3 categorical covariates (time as defined by weekly part A visits, presence of type 2 diabetes mellitus at part A baseline, and presence of heart failure at part A baseline), part A baseline central serum potassium as a continuous covariate, and an unstructured covariance structure. Estimates for the starting dose groups come from running the longitudinal model separately on the cohort of patients in each dosing group. If a central serum potassium result was missing at a visit, it was imputed by the regression model and the local laboratory result from that particular visit. No other imputation was used.

[b]The P value comes from a test comparing the mean change in serum potassium at part A week 4 with zero.

[c]The estimated percentage and standard errors are stratified by the presence or absence of heart failure, the presence or absence of type 2 diabetes mellitus, and central part A baseline serum K^+ (< 5.5 mmol/L or ≥ 5.5 mmol/L).

[d]Reason for failure may include either not completing part A or part A serum potassium < 3.8 mmol/L or ≥ 5.1 mmol/L.

Source: OPAL-HK Clinical Study Report.[8]

Another potential source of bias was regression to mean, which the sponsor considered as random error in the measurement of serum potassium and attempted to control by multiple measurements taken locally and centrally. However, this procedure did not take into account fluctuations in serum potassium over time, which could also result in regression to the mean if patients are selectively sampled at a peak severity in the natural history of a disease that has a tendency to return to average severity levels over time, regardless of interventions administered. While baseline serum potassium value was included in the regression model for primary analysis, this would help control for regression to the mean but may not fully eliminate the bias from the results. One key limitation in part A with respect to external validity was the highly selective criteria used to enrol only patients without significant comorbidities and with a serum potassium of 5.1 mmol/L to less than 6.5 mmol/L. The clinical expert

Table 3: Summary of Key Efficacy Results — OPAL-HK Part B (ITT Population)

Key efficacy results	Placebo N = 52	Patiromer N = 55
Change in serum potassium from part B baseline to part B week 4 or the first target serum potassium range of < 3.8 mmol/L or ≥ 5.5 mmol/L[a]		
Serum potassium at part B baseline, mean (mmol/L)[b]	4.45 (0.34)	4.49 (0.43)
Estimated change in serum potassium, median (quartiles)[c]	0.72 (0.22 to 1.22)	0.00 (−0.30 to 0.30)
Difference in median change (95% CI)[d]	0.72 (0.46 to 0.99)	
P value	< 0.001	
Secondary efficacy outcome results		
Serum potassium ≥ 5.5 mmol/L, stratified percentages (95% CI)[e]	60 (47 to 74)	15 (6 to 24)
Difference (95% CI)[f]	45 (29 to 61)	
P value	< 0.001	
Serum potassium ≥ 5.1 mmol/L, stratified percentages (95% CI)	91 (83 to 99)	43 (30 to 56)
Difference (95% CI)[f]	48 (33 to 63)	
P value	< 0.001	

ANOVA = analysis of variance; CI = confidence interval; FOS = for oral suspension; ITT = intention to treat; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.

[a]Changes from baseline serum potassium were ranked, and the treatment groups were compared using an ANOVA model with strata used at randomization (part A baseline serum potassium [< 5.8 mmol/L or ≥ 5.8 mmol/L] and presence of type 2 diabetes mellitus [yes/no]) included as covariates in the model and a variable for the treatment group.

[b]Data taken from safety set.

[c]The estimates of median change and quartiles in the patiromer group were calculated as the median of patiromer medians and median of the quartiles from the 10 complete-observation datasets created through multiple imputation. The placebo median was calculated by adding the Hodges-Lehmann difference to the RLY5016 FOS median. The quartile changes of the placebo group were calculated as the median quartiles shifted by the difference (0.08) between the Hodges-Lehmann estimate (0.72) and the median of the medians of the placebo group (0.80).

[d]To compare patiromer with placebo, the difference between the mean ranks was tested using a 2-sided t-test. The difference and 95% CI between the treatment groups in median change from baseline was estimated using a Hodges-Lehmann estimator. The statistical tests and estimates were calculated for each of the 10 complete-observation datasets and combined using multiple imputation methods.

[e]The estimated percentages and standard errors are stratified by the presence or absence of type 2 diabetes mellitus and central part A baseline serum potassium level (< 5.8 mmol/L or ≥ 5.8 mmol/L).

[f]The treatment groups were compared with a Mantel-Haenszel test stratified by the 4 randomization strata. Missing centrally measured serum potassium results were imputed using either the local laboratory values and the regression model or multiple imputation. Multiple imputation yielded 10 complete-observation datasets for this analysis. The statistical tests and estimates were calculated for each of the 10 complete-observation datasets and combined using multiple imputation methods.

Source: OPAL-HK Clinical Study Report.[8]

consulted for this review indicated that patients with mild hyperkalemia, especially those with less than 5.5. mmol/L, may not always be treated in a clinical setting, particularly with a separate drug such as patiromer instead of adjusting an RAASi or other medications.

In part B, randomization appeared to have been done appropriately, with no notable difference in baseline characteristics and dropouts. Patients were blinded to their treatment assignment throughout the study; study personnel involved with the handling and processing of blood specimens, assessment of serum potassium in the central laboratory, and statisticians involved in data analysis also remained blinded throughout the study or until the database was locked. However, there is a possibility of potential unblinding of the patients due to the different titration algorithms followed for placebo and patiromer, as well as differences in the taste, texture, and weight of the 2 treatments. Although the outcome measures were based on objective laboratory values, such potential unblinding could have changed patient behaviours (changes in diet, interaction with health professionals), which could, in turn, affect patients' serum potassium values over time and thus the validity of the results. Strengths included adequate power for the primary end point (> 90%), which allowed the exploration of effects of patiromer across various subgroups, with results from the subgroup and sensitivity analyses confirming the findings of the primary efficacy analyses, well balanced baseline characteristics, and no differential dropouts.

A major limitation of the generalizability of the findings in part B is related to the enrichment design, i.e., allowing only responders to patiromer treatment (those who achieved serum potassium within 3.8 mmol/L and < 5.1 mmol/L in part A) to enter into part B. The reported rationale for the 2-part design in OPAL-HK with a single-arm treatment phase and placebo-controlled withdrawal phase was that it served as 1 of the 2 pivotal studies required for market authorization. As well, starting 1 group of patients with placebo would be considered unethical and unsafe, since all patients entering the study were hyperkalemic. Nonetheless, the selection of responders may augment treatment benefits while minimizing side effects, something that may not occur to the same extent in an unselected (non-enriched) patient

Table 4: Adverse Events — OPAL-HK Part A and B (Safety Set)

	Part A			Part B	
	Dose group 1 5.1 mmol/L to < 5.5 mmol/L	Dose group 2 5.5 mmol/L to < 6.5 mmol/L	Total 5.1 mmol/L to < 6.5 mmol/L	Placebo	Patiromer
Adverse events	N = 92	N = 151	N = 243	N = 52	N = 55
Patients with ≥ 1 AEs, n (%)	42 (46)	72 (48)	114 (47)	26 (50)	26 (47)
SAEs					
Patients with ≥ 1 SAEs, n (%)	1 (1)	2 (1)	3 (1)	1 (2)	0
WDAEs					
WDAEs, n (%)	5 (5)	10 (7)	15 (6)	1 (2)	1 (2)
Dose modification, n (%)	6 (7)	16 (11)	22 (9)	1 (2)	1 (2)
Deaths					
Number of deaths, n (%)	0	0	0	1 (2)	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: OPAL-HK Clinical Study Report.[8]

population. Likewise, the high compliance seen in the trial may, in part, be a result of the enrichment design.

Overall, the short duration of the trial (12 weeks) and the choice of serum potassium as the basis for all efficacy end points also limited the generalizability of the results. While AMETHYST-DN provided longer-term efficacy and safety data (see Other Relevant Evidence), the effect of patiromer on clinical end points, such as major advanced cardiac or kidney events, hospitalization, mortality, and quality of life, is uncertain. It is unclear if the benefits in the management of serum potassium in the short-term would translate to clinical benefits over the long-term and prevent serious hyperkalemic events that could be fatal or require hospitalization.

Indirect Comparisons

No evidence from indirect comparisons was available.

Other Relevant Evidence

AMETHYST-DN was a multi-centre, randomized, open-label, dose-ranging, phase II study for the use of patiromer to treat patients with hyperkalemia. The study consisted of an 8-week treatment initiation period (TIP) followed by a 44-week long-term maintenance period (LTMP). The primary efficacy outcome was the change in serum potassium from baseline to the time before dose titration or week 4. The primary safety outcome for the LTMP was the frequency and severity of AEs.

Patients were eligible if they were between 30 and 80 years old, had T2DM, CKD, and were receiving ACEi and/or ARB medications. Exclusion criteria included a body mass index (BMI) of 40 kg/m^2 or greater, heart failure (New York Heart Association [NYHA] class III or IV), severe GI disorders, or use of the following: loop or thiazide diuretics, other antihypertensive medications, polymer-based drugs, phosphate binders, other potassium binders, or potassium-sparing medication.

Patients (N = 304) were randomly assigned to 1 of 2 strata based on baseline serum potassium levels (> 5.0 mmol/L to 5.5 mmol/L or > 5.5 mmol/L to < 6.0 mmol/L). Patients in stratum 1 received patiromer 8.4 g/day, 16.8 g/day, or 25.2 g/day, whereas those in stratum 2 received patiromer 16.8 g/day, 25.2 g/day, or 33.6 g/day. Note that the 33.6 g/day dose is outside the Health Canada–approved dose range. Over the course of the entire study treatment period, patients were exposed to patiromer for a mean (SD) of approximately 265 (138.35) days. The mean (SD) serum potassium measurements at baseline were 5.15 mmol/L (0.251 mmol/L) and 5.66 mmol/L (0.359 mmol/L) for strata 1 and 2, respectively. At week 4, the mean (SD) change from baseline levels was −0.47 mmol/L (0.601 mmol/L) and −0.92 mmol/L (0.748 mmol/L) for the 2 strata. At the end of treatment, the mean (SD) levels for strata 1 and 2 were 4.61 mmol/L (0.429 mmol/L) and 4.57 mmol/L (0.549 mmol/L), respectively. At 28 days post treatment, serum potassium increased once again for both, by a mean of 0.43 mmol/L (0.456 mmol/L) for stratum 1 and 0.49 mmol/L (0.685 mmol/L) for stratum 2.

Overall, 65.8% of patients in stratum 1 and 77.4% of patients in stratum 2 experienced an AE. GI-related AEs occurred less frequently in stratum 1 (9.1%) compared with stratum 2 (14.3%). During the TIP, though, the opposite was true for the LTMP: 10.6% for stratum 1 and 9.1% for stratum 2. SAEs were reported in 13.2% and 17.9% of patients in strata 1 and 2, respectively, but SAE GI disorders were infrequent.

AMETHYST-DN was a multi-centre, open-label study of patiromer with no active comparator or placebo. Patients were randomized to different doses of patiromer, but there was no blinding of treatment, and the observed efficacy may be at high risk of bias. Some limitations may also prevent the results from being generalized to practice settings in Canada, given that not all of the patients in stratum 1 with serum potassium levels of less than 5.5 mmol/L would be treated. As well, eligibility was restricted to patients who were between 30 and 80 years old, diagnosed with T2DM and CKD, and who had a BMI no greater than 40 kg/m^2. Patients could not have a serum potassium greater than 6.0 mmol/L and, although 35% of patients reported having NYHA class I or II heart failure, those with NYHA class III or IV were excluded. Therefore, it may not be reasonable to extend the safety and efficacy results to individuals with hyperkalemia outside of these criteria without further investigation into these populations.

Conclusions

The efficacy and safety of patiromer was assessed in a 12-week single-blind, phase III trial, with supportive evidence provided by an open-label, dose-ranging, phase II trial with 1 year of follow-up data. Based on evidence from the phase III trial, 4 weeks of patiromer treatment at 8.4 g/day and 16.8 g/day reduced serum potassium to a clinically meaningful level among hyperkalemic patients (baseline serum potassium of between 5.1 mmol/L and 6.5 mmol/L) who had CKD (baseline eGFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2) and who were on RAASi treatment. More than 70% of these patients achieved a normal level of serum potassium (3.8 mmol/L to < 5.1 mmol/L). Further continuation of patiromer for 8 weeks resulted in the maintenance of normal serum potassium in these patients, whereas withdrawal from patiromer led to a recurrence of hyperkalemia. A large proportion of patients were able to continue patiromer and RAASi treatment (94%), of which only 6% required RAASi dose modification or discontinuation. The biggest limitation of the trial was the highly selective criteria for including patients, who were chosen based on an absence of significant or unstable comorbidities (other than CKD and manageable diabetes and heart conditions), as well as their response to patiromer treatment. The effects observed may therefore not be generalizable to the larger population of patients. Additionally, the effects were primarily observed in mildly hyperkalemic patients; therefore, it is unclear if patients with moderate or severe hyperkalemia (serum potassium > 6.0 mmol/L) would respond to patiromer to the same extent. It is also uncertain if controlling serum potassium would translate into clinical benefits, notably, preventing major cardiac or kidney events and hospitalization. Few AEs and SAEs were reported, although the short duration of the trial and selecting only patients who showed a response to treatment limited the trial's ability to detect any safety signal with confidence. Nonetheless, safety data from the longer-term, phase II trial and the Health Canada safety evaluation also did not identify clear safety concerns. Most AEs were GI-related. There were no direct or indirect comparisons of patiromer with other potassium binders or treatments for hyperkalemia, and placebo is unlikely to be the best comparator; therefore, the comparative benefit and safety of this medication is unknown. Overall, patiromer appears to be effective in reducing serum potassium in patients with mild hyperkalemia and CKD and has no major safety concerns; however, its effect on clinical end points in less certain, particularly among patients with moderate or severe hyperkalemia.

Introduction

Disease Background

Potassium is an essential element in the human body with many physiologic functions. A key function is to determine the membrane potential of all cells in the body, required for conducting electrical impulses and maintaining normal cell electrophysiology.[4] The level of potassium is therefore tightly regulated by homeostatic mechanisms. Hyperkalemia refers to an elevated level of extracellular potassium, i.e., in plasma or serum, typically greater than 5.0 mmol/L. The normal plasma concentration of potassium is between 3.5 mmol/L and 5.0 mmol/L. Hyperkalemia is classified as mild, moderate, or severe, with corresponding serum potassium values of 5.0 mmol/L to 5.9 mmol/L, 6.0 mmol/L to 6.4 mmol/L, or greater than 6.5 mmol/L, respectively.[1] Hyperkalemia is primarily caused by increased potassium release from the cells and reduced urinary potassium excretion, both of which may result from various clinical conditions (most commonly acute or chronic renal failure) or may be induced by medications.

The physiologic manifestations of hyperkalemia include muscle weakness or paralysis, cardiac conduction abnormalities (e.g., QRS widening), and cardiac arrhythmias (such as ventricular fibrillation), which can be life-threatening and may even lead to sudden death.[9] Risk factors associated with hyperkalemia include the following: reduced renal function, heart failure, diabetes mellitus, older age, and the administration of drugs that act on the renin-angiotensin-aldosterone system (RAAS), such as ACEis, ARBs, aldosterone antagonists, and renin inhibitors.[2] In healthy individuals, potassium balance is regulated by the kidneys, which excrete 90% to 95% of potassium. Patients who have impaired kidney function, such as those with CKD and end-stage renal disease, experience a decrease in urinary excretion of potassium, consequently increasing the serum potassium level. CKD is defined as the presence of kidney damage or reduced kidney function for at least 3 months, with measured or estimated eGFR of less than 60 mL/min/1.73 m^2.[1]

In Canada, it has been estimated that between 1.3 million and 2.9 million people have CKD; however, that estimate is almost 2 decades old.[10] A recent study estimated that the prevalence of CKD in patients in primary care in Canada is 71.9 per 1,000 individuals (approximately 2.7 million people), using a national chronic disease surveillance system. CKD prevalence increases among individuals with 3 or more other chronic diseases (281.7 per 1,000).[3] For hyperkalemia, the incidence and prevalence in the general population is unclear, since this is often a transient condition and longitudinal studies to monitor for its presence are unavailable. One Canadian study reported that 2.6% of ED visits and 3.5% of hospital admissions were associated with hyperkalemia, based on an analysis among elderly patients in Southwestern Ontario from 2003 to 2010.[4] The incidence of hyperkalemia may be higher in patients with CKD, and patients on maintenance dialysis may have the highest incidence.[4]

Standards of Therapy

The management of hyperkalemia depends on the acuity and the severity (i.e., degree of potassium elevation) of the event. Acute hyperkalemia occurs when potassium is released from cells, which can happen in states of trauma, metabolic acidosis, or hemolysis, and requires immediate intervention. In a systematic review published by the Canadian Medical Association, the following are commonly used for acute management of hyperkalemia: insulin, beta2-adrenergic agonists (inhaled, nebulized, and IV administration), bicarbonate,

resins, fludrocortisone, aminophylline, and dialysis.[5] Chronic hyperkalemia occurs when there is an impairment in potassium excretion (e.g., kidney disease) and/or an increase in potassium load (e.g., a diet high in potassium or supplements), and requires ongoing management. Severe hyperkalemia (> 6.5 mmol/L) due to either acute or chronic cause is considered a medical emergency. In such a setting, patients should be hospitalized and treated with IV therapies to rapidly redistribute potassium into cells (e.g., insulin plus glucose, sodium bicarbonate, beta-adrenergic agonists), stabilize the cell membrane (e.g., IV calcium), or remove potassium from the body (e.g., hemodialysis or IV loop diuretics).[6]

Mild or moderate forms of acute or chronic hyperkalemia may be treated with drugs that increase potassium excretion, such as oral loop or thiazide diuretics and cation-exchange resins or cation-exchange polymers. This latter group of medications, also known as potassium binders, include SPS, CPS, and patiromer. The potassium binders cannot be used for hyperkalemia that is a medical emergency, due to their delayed onset of action.[6]

Non-pharmacological modalities are also important in the management of hyperkalemia. The first step in the management of mild or moderate hyperkalemia may include dietary modification to reduce potassium intake, discontinuation of potassium supplements, and discontinuation or a reduction in dose of medications that increase potassium, such as an RAASi.[4] While discontinuation or a reduction in RAASi dose may help to normalize potassium levels, this can result in patients losing the renal- and cardio-protective effects of these medications and, therefore, is not desired. Drugs that affect renal function (ACEis, ARBs, MRAs) might affect serum potassium; therefore, these drugs should be used with great care and patients should limit potassium intake from dietary sources.[11]

Drug

Patiromer is a non-absorbed, cation-exchange polymer that acts by increasing fecal potassium excretion through the binding of potassium in the lumen of the GI tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, thereby reducing serum potassium levels. Patiromer is available as a powder for oral suspension in the following doses: 8.4 g, 16.8 g, and 25.2 g (as patiromer sorbitex calcium). The recommended starting dose of patiromer is 8.4 g once daily, which can be adjusted by 8.4 g in weekly intervals, up to a maximum dose of 25.2 g once daily, based on the serum potassium level and the desired target range. Patiromer may be taken with or without food and should be suspended in a liquid before administration; the method of reconstitution is provided in the product monograph.[7]

Patiromer (as patiromer sorbitex calcium) initially received a Notice of Compliance from Health Canada on October 3, 2018, which was revised on February 28, 2020. It is indicated for the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2).[7] The sponsor requested reimbursement for patients with CKD stage 3 to 4 on RAASi therapy, consistent with the population in the pivotal trial submitted for this review.[12]

Table 5 provides the key characteristics of patiromer, SPS, and CPS, which are the other potassium binders approved by Health Canada for the treatment of hyperkalemia.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

One submission from the patient group the Kidney Foundation of Canada was received for this review. The Kidney Foundation of Canada is a national volunteer organization committed to eliminating the burden of kidney disease and helping patients achieve excellent kidney

Table 5: Key Characteristics of Patiromer and Other Treatments

Characteristic	Patiromer	SPS	CPS
Mechanism of action	Cation-exchange polymer: Binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with calcium-sorbitol complex)	Cation-exchange resin: Binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with sodium ions)	Cation-exchange resin: Binds potassium in the intestine and increases excretion of potassium through feces (exchange of potassium with calcium ions)
Indication[a]	Treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2)	Treatment of hyperkalemia	Treatment of hyperkalemia (anuria or severe oliguria, acute and chronic renal failure, dialysis)
Route of administration	Oral suspension	Oral suspension or enema	Oral suspension or enema
Recommended dose	Starting dose of 8.4 g once daily to a maximum of 25.2 g once daily	Oral: 15 g 1 to 4 times daily Rectal: 30 g to 50 g once or twice daily	Oral: 15 g 3 to 4 times daily Rectal: 30 g once daily
Serious adverse effects or safety issues	GI symptoms Hypokalemia	Intestinal obstruction Intestinal rupture (diarrhea may need to be induced to prevent these safety issues) Hypokalemia	GI injury (most cases occurred with concomitant use of sorbitol) Hypokalemia
Other	Not used for rapid reduction of potassium due to delayed onset of action (4 to 7 hours) Non-specific binder that binds magnesium, which can cause hypomagnesemia Contraindicated in patients with hereditary condition of fructose intolerance (contains sorbitol)	Not used for rapid correction of severe hyperkalemia Non-specific binder that binds calcium and magnesium in addition to potassium, which can cause hypocalcemia or hypomagnesemia GI side effects are common Not administered on a chronic basis	Non-specific binder that binds magnesium in addition to potassium, which can cause hypomagnesemia; also risk of hypercalcemia due to calcium content

CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; NOC = Notice of Compliance; SPS = sodium polystyrene sulfonate.

[a]Health Canada–approved indication.

Source: Product monographs for SPS,[13] CPS,[14] and patiromer.[7]

health and optimal quality of life in hopes of a cure. The organization is committed to funding and stimulating innovative research for better treatments and a cure, providing education and support to prevent kidney disease in those at risk and empowering those with kidney disease to optimize their health status, advocating for improved access to high-quality health care, and increasing public awareness and commitment to advancing kidney health and organ donation.

The Kidney Foundation of Canada collected patient input in October and November of 2020 through self-administered questionnaires offered in English and French to individuals across Canada. The survey was directed at people living with CKD and their caregivers. The survey included questions inquiring about respondents' lived experience with CKD and medications and expectations for new drug therapies in Canada; additionally, there were questions specific to patiromer. The survey was promoted through the Kidney Foundation's social media channels (Twitter and Facebook), website, and e-newsletter. A total of 33 people responded to the survey, which resulted in 15 completed and 18 partially completed surveys. Nine respondents identified as being a person living with CKD and 5 identified as being a caregiver for a person with CKD. Among the respondents who reported their current age or the current age for the person they care for, 1 was under 14 years old, 1 was 25 to 39 years old, 9 were 55 to 69 years old, and 1 was more than 70 years old. Further, 13 respondents reported their duration living with CKD: 1 respondent for less than 1 year, 1 respondent for 1 to 2 years, 2 respondents for 3 to 5 years, 2 respondents for 6 to 10 years, 2 respondents for 11 to 20 years, and 5 respondents for more than 20 years.

Disease Experience

The Kidney Foundation of Canada noted that kidney disease is a risk factor for hyperkalemia. There are usually no specific symptoms of kidney disease until the damage is severe; nevertheless, kidney disease is often associated with other medical conditions such as diabetes, high blood pressure, and heart disease. This is reflected in the survey results, as 86% of respondents reported experiencing high blood pressure, 72% reported high potassium levels, 86% reported low hemoglobin levels, and 93% reported low iron levels.

CKD negatively impacts the physical and/or mental health and the daily routine, especially the career, of both patients and caregivers. In the words of 1 patient: "CKD has affected me the (sic) and my spouse significantly from PKD and family members, Transplant to rejection to 24 years on Hemodialysis but never giving up! If you can imagine being diagnosed at 20 waiting for your kidneys to fail, not having children, Bi lateral (sic) nephrectomy, spinal fusion, osteoarthritis, not being able to continue my working career and much more." Further, the chronic nature of the disease and associated fatigue and sleep difficulties were highlighted. One patient stated "2.5 years on dialysis — now 24 years posttransplant. Still working after 44 years — fatigue and sleep problems have been huge issues last 10 years. But still well." Another noted "I'm missing lots of school because I need to go to [hospital name removed] lots. This makes me very sad. I hate taking so much (sic) medications everyday. I am afraid my scars and stretch marks will never go away." For caregivers, the impact on mental health also arises from seeing the person they are providing care for experience pain and feelings of depression. One caregiver stated, "When I'm done caring for my spouse I'm too tired to do things for me like seeing friends or going to lunch- between taking him to dialysis and the house chores it's tiring" and another said "I have a hard time with keeping him on track with meds, with diet and with everyday life! He is tired all the time, he does not sleep well, he has a lot of pain and some swelling of his joints. He is depressed. It's sad, it breaks my heart."

Experience With Treatment

The survey reported that 64% of respondents were currently under a dietary restriction and 22% had a dietary restriction in the past but not anymore for high potassium. Ninety-three percent of respondents indicated they follow a special diet to manage high potassium. Fifty percent of respondents reported taking medication for high potassium; namely, 4 respondents had taken SPS, 2 had taken CPS, and 3 had taken patiromer. Among respondents currently taking medication for high potassium levels, 1 indicated they were "satisfied," 2 were "neither satisfied nor unsatisfied," and 3 were "unsatisfied." The key reasons for dissatisfaction with treatment were taste, frequency of administration, and constipation.

People on dialysis usually need to limit potassium intake to avoid hyperkalemia between treatments. This diet is highly restrictive and negatively impacts quality of life. Additionally, Canadians living with kidney failure and their families face significant financial challenges due to out-of-pocket costs, which is compounded by loss of income. For some families, this results in a state of poverty; thus, these patients are not able to optimally manage their medical issues (i.e., poverty is a social determinant of health). Financial implications are particularly challenging with dialysis, which is often associated with a decrease in income (e.g., inability to work) and increase in out-of-pocket costs (e.g., medication and transportation to treatment). Government coverage and financial support for people on dialysis varies, resulting in inequalities across jurisdictions. Additionally, the Kidney Foundation of Canada noted that those living with kidney failure tend to be part of a low-income and high-cost population.

The following were identified by survey respondents as "very important" or "important" factors when choosing CKD medications: fatigue, interference with sleep and other medications, edema of the foot, effect on mood, changes in appetite, cost, and length of time on the medication. Other factors of consideration included side effects, impact on health, effectiveness, and interactions with other medications; in the words of 1 respondent, "one that does not add to the burden of other symptoms or does not increase the risk of long-term complications. Reduce symptoms, prolong life and QUALITY OF LIFE."

The Kidney Foundation of Canada also reported on the experiences of patients with patiromer. None of the 3 respondents with experience taking patiromer had switched from another medication and all had accessed patiromer through private insurance (i.e., prescription coverage). Two respondents noted that their potassium levels had improved since starting patiromer. One respondent noted that they hated the taste of patiromer. Among the 3 respondents, there were differing reports on the effect of patiromer on symptoms. Regarding tiredness or weakness, 1 respondent reported that it improved, whereas the other 2 reported that it was worse. Regarding nausea or vomiting, 1 respondent noted it was better, 1 reported it being the same, and 1 reported it being worse. Regarding trouble breathing, 2 respondents noted that it was about the same while 1 stated that it was better. Regarding swelling, 1 respondent reported it being much better, 1 noted it was better, and 1 noted it was worse. Regarding irregular heartbeat, 1 respondent reported that it was much better, 1 reported it being about the same, and 1 did not know. The Kidney Foundation of Canada stated that patiromer may help people achieve better health outcomes and improve their quality of life. Accordingly, it should be available as a treatment option for people living with CKD to help manage serum potassium levels.

Improved Outcomes

The Kidney Foundation of Canada survey respondents would like to see new therapies that are affordable, effective, associated with minimal side effects, convenient to administer (e.g., frequency and ease), ease life with CKD, and provide a good quality of life. Additionally, the patient group highlighted that to address the financial burden and minimize disparities in accessing medications for people with kidney disease, mechanisms need to be developed to offset costs equitably across jurisdictions.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). The following input was provided by 1 nephrologist with expertise in the diagnosis and management of kidney disease.

Description of the Current Treatment Paradigm for the Disease

The following 3 factors contribute to the incidence of hyperkalemia: CKD, differences in dietary intake of potassium, and co-administration of pharmacologic treatments (drugs directly or indirectly used for CKD prevention). Hyperkalemia is treated initially by withdrawing drugs that increase potassium, namely the RAASis and MRAs. The problem with this approach is that patients lose the protection that these drugs confer on the cardiovascular and renal systems. Other treatments for chronic hyperkalemia are diuretics (which may have deleterious effects associated with electrolyte disturbance), laxatives, and potassium binders. All approaches will include counselling patients about moderating their intake of potassium-containing foods.

Treatment Goals

The goal of treatment is to avoid life-threatening arrhythmias and enable optimal dosing of an RAASi.

Unmet Needs

The withdrawal or dose reduction of an RAASi compromises the care of patients with cardiovascular or renal disease and leaves patients at increased risk of worse clinical outcomes.

Place in Therapy

Patiromer would be used as an adjunctive treatment for patients who require an RAASi and who have experienced hyperkalemia. Prior to initiating therapy with patiromer, clinicians would need to first understand the contributing causes of hyperkalemia and address those factors that are readily modifiable, such as reversible causes of impaired kidney function, diets high in potassium, and RAASi use. This drug may be considered once all reversible causes have been addressed, especially in patients who require continuation of RAASi therapy, but also in other patient populations who remain hyperkalemic despite optimal management of the condition.

Patient Population

The patients most in need of patiromer are those who experience hyperkalemia while on an RAASi. To identify patients best suited for treatment, laboratory tests to measure serum potassium would be needed, as this is often the only way to detect hyperkalemia. Patients with serum potassium greater than 5.5 mmol/L would be considered for treatment.

Assessing Response to Treatment

Response to treatment would be assessed with serial blood testing of serum potassium. Assessments would initially be monthly, and then quarterly once potassium levels become stable. Serum potassium is the immediate assessment of treatment response. However, the most clinically relevant outcome would be continued optimal use of an RAASi to confer cardiovascular and renal protection. This would also be important to patients because they would have peace of mind knowing they can continue on RAASi therapy without worry of hyperkalemia.

Discontinuing Treatment

If RAASi therapy is withdrawn (e.g., no longer indicated), then therapy with patiromer may be discontinued. If dialysis is initiated for kidney failure, then patiromer may be discontinued, because dialysis will generally remove potassium. However, there may be cases when patients on dialysis require continued treatment for hyperkalemia.

Prescribing Conditions

Specialists in cardiology, nephrology, endocrinology, or general internal medicine are required to diagnose, treat, and monitor patients with hyperkalemia. Patiromer, therefore, should be prescribed by specialists in community or hospital-based clinics.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

Clinician input on the review of patiromer was provided by 1 individual clinician at Sunnybrook and 1 group clinician input on behalf of 10 clinicians at the Scarborough Regional Nephrology Program at Scarborough Health Network. Both inputs were received from clinicians working in Ontario. Information for the individual clinician input was gathered through patients in emergent, ambulatory, and in-hospital settings. The group clinician input was collected from a sample of 519 office patients with hyperkalemia (with a serum potassium of 5.5 mmol/L or greater). Of these patients, 117 were receiving SPS as of January 2020.

Unmet Needs

The individual clinician input noted that the current treatments for hyperkalemia include diet, diuretics, sodium bicarbonate, dialysis, SPS, and CPS. The individual clinician input noted that the lack of efficacy of current treatments leads to high potassium levels. The clinician also noted that SPS is “highly unpleasant” and is linked to bowel necrosis in a small number of patients. The group clinician input noted that SPS is also associated with a high sodium load and is potentially harmful for patients with cardiovascular disease. The individual clinician input added that the current available therapies do not reliably lower serum potassium to the normal range in the acute setting. In the chronic setting, patient’s serum potassium cannot be maintained in a normal range with any efficacy.

The clinicians noted that treatment goals for patients with hyperkalemia is to optimize medical therapy for cardiac conditions, potentially reducing mortality and decreasing hospitalization and ED visits.

The clinician group noted that hyperkalemia can result from renal failure, especially diabetic nephropathy, and from drug treatments, such as ACEis, ARBs, and spironolactone. The individual clinician input added that use of current treatments is not evidence-based and, other than dialysis, do not have data supporting long-term safety or efficacy. The clinician also noted that current treatments do not impact the underlying disease mechanism and only target the hyperkalemia. However, the clinician noted that for some patients, these treatments are life-saving and prevent hyperkalemia. The clinician noted that these treatments preserve lifestyle and allow these patients to have diets closer to what they are more familiar with, especially important for elderly patients.

Both clinician inputs noted that patients with the greatest unmet need are those with CKD and those with heart failure who require cardiac and renal treatments, such as ACEis, ARBs, or MRAs.

Place in Therapy

Both the individual and group clinician input suggested that patiromer will cause a shift in the current treatment paradigm, as the current paradigm is not evidence-based, with regional variation in practices. The clinician also noted that the current treatment paradigm is largely unproven as being effective in practice and is associated with important safety concerns. As well, patiromer may allow for patients to remain on appropriate dosing of ACEis, ARBs, or MRAs and angiotensin receptor-neprilysin inhibitors that are also associated with improved renal and cardiovascular outcomes.

The clinician input noted that initial treatment would be to control serum potassium through modified diet. Patiromer would be added to dietary restriction of potassium in patients who remain hyperkalemic. Dialysis should be initiated if the potassium is “dangerously” high, and the newer treatments can keep the patients safe until dialysis.

The individual clinician input noted that patiromer is most appropriate for patients with a longer-term need for managing serum potassium levels, especially those who require optimal dosing of ACEis, ARBs, or MRAs. Patients with normal potassium levels are least suited for treatment with patiromer.

Patient Population

The clinician input noted that patients with acutely elevated serum potassium levels and those with chronic hyperkalemia who are unable to remain on appropriately dosed ACEis, ARBs, or MRAs are in need of new treatments; the latter would benefit the most from a treatment like patiromer. Therefore, patients with kidney failure and heart failure are most likely to exhibit a response to treatment with patiromer.

Patients with hyperkalemia can be identified using routine laboratory testing of serum potassium in high-risk patients before initiating treatments; these patients may be those with CKD and diabetes or heart failure and receiving treatment with MRAs, ARBs, or ACEis.

Assessing Response to Treatment

A laboratory test to measure serum potassium levels and the normalization of serum potassium would be considered a meaningful response to treatment. The expectation is

that patiromer will allow clinicians to optimize therapeutic treatment for the aforementioned patients. Achieving this goal would be a clinically important outcome because of the associated renal- and cardiac-protective effects of MRAs, ARBs, and ACEis that impact survival.

Patients would be monitored with regular, planned laboratory testing to assess response and to ensure patients have a stable potassium level.

Discontinuing Treatment

The individual clinician input suggested that treatment with patiromer should be discontinued once a patient's serum potassium is within the normal range, with less frequently dosed therapy. The clinician group input noted that treatment with patiromer should be discontinued when a patient's kidney disease progresses to requiring dialysis. The group noted that even when the patient progresses to dialysis, continuing patiromer treatment may reduce the frequency of dialysis by maintaining stable potassium levels.

Prescribing Conditions

The clinician inputs indicated that patiromer could be prescribed in the community setting; a specialist is not required to diagnose, treat, and monitor patients who might receive patiromer. Patiromer should be used as indicated; this would primarily target patiromer for patients with CKD and diabetes or heart failure who are being treated with any ARB, ACEi, or MRA and experiencing hyperkalemia. The input also noted that for the acute setting, patiromer should be prescribed for patients with elevated potassium (up to 6.4 mmol/L) to treat the patient and keep them from requiring a visit to an ED. In the ED, patients with hyperkalemia could be given patiromer to lower their potassium without the need for dialysis. Additionally, in the hospital setting, patiromer can be used to lower potassium in admitted patients and avoid the need for dialysis.

Additional Considerations

The group clinician input emphasized that hyperkalemia presents a challenge to the management of kidney and cardiovascular disease. They noted that a stable and optimal level of potassium will allow patients to receive other treatments that reduce morbidity and mortality.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 6.

Clinical Evidence

The clinical evidence included in the review of patiromer is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes additional relevant sponsor-submitted

studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of patiromer (as patiromer sorbitex calcium: 8.4 g, 16.8 g, and 25.2 g patiromer, oral suspension) for the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2).

Table 6: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
How is hyperkalemia defined and at what threshold of serum potassium would patients be treated? OPAL-HK enrolled patients included those with serum potassium levels of 5.1 mmol/L to < 5.5 mmol/L; would these patients be treated?	Although clinical factors other than a serum potassium level at a specific point guide treatment, in general, patients with serum potassium > 5.5 mmol/L would be considered for treatment.
Patients in OPAL-HK had to be receiving RAASi therapy for at least 28 days before enrolment. Should this be a condition for use? What duration and dose of RAASi therapy is appropriate?	A large percentage of patients who would be prescribed patiromer in practice would require treatment with an RAASi. Patiromer could enable the continued use of an RAASi. Therefore, patiromer would be used as an adjunctive treatment for patients who require RAASi blockers who have demonstrated problems with hyperkalemia.
Patients in OPAL-HK had to have an eGFR of 15 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 for enrolment. Should this be a condition for use?	The eGFR cut-offs are fluid in nature. Off-label use of patiromer may be expected in dialysis and non-dialysis and transplant CKD patients with eGFR < 15 mL/min/1.73 m^2, even if the drug is reimbursed based on the Health Canada indication.
Should there be a requirement that patients have tried other treatments for hyperkalemia before receiving patiromer?	Before starting patiromer, the causes contributing to hyperkalemia should be addressed first: diet modification, optimization of kidney function (if possible), and medication adjustment. If kidney function and diet have been optimized and it is determined there is a strong clinical rationale for the patient to remain on an RAASi, patiromer may be seriously considered as an adjunctive therapy to prevent elevations in potassium. Furosemide, sodium polystyrene sulfonate, or laxatives have numerous issues with administration and adverse effects and are not optimal treatments for the sole purpose of lowering serum potassium. Therefore, requiring patients to use 1 of these before trying patiromer would NOT be the preferred approach.
What percentage of patients do you expect to use the highest dose of 25.2 g daily?	This is difficult to determine and would depend on the ability to regain and/or maintain optimal RAASi dosing.
How long would patients typically require treatment with patiromer? Would they be anticipated to frequently stop and restart?	It is expected that if RAASi therapy is withdrawn (e.g., no longer indicated), or if dialysis is initiated for kidney failure, then therapy with patiromer may be discontinued. Patiromer therapy is expected to continue until such requirements. If RAASi therapy is reinstituted or dialysis is no longer required, then re-administration of patiromer may be considered, based on clinical judgment.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAASi = renin-angiotensin-aldosterone system inhibitor.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 1. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[15]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid and Embase (1974–) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Veltassa or patiromer. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, the WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on November 27, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 21, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[16] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 1 study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 8. A list of excluded studies is presented in Appendix 2.

Table 7: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adults with hyperkalemia who have CKD (eGFR ≥ 15 mL/min/1.73 m^2). Subgroups: • severity of hyperkalemia (in mmol/L): mild (5.5 to 5.9), moderate (6.0 to 6.5), severe (> 6.5) • number of previous hyperkalemic events • patients on RAASi therapy (i.e., ACEi or ARB) or MRA therapy (i.e., spironolactone) • patients with other comorbidities including HF, CAD, or diabetes mellitus • eGFR level (in mL/min/1.73 m^2): mild reduction (60 to 89), mild to moderate reduction (45 to 59), moderate to severe reduction (30 to 44), severe reduction (15 to 29)
Intervention	Patiromer oral suspension (patiromer sorbitex calcium) 8.4 g once daily up to a maximum of 25.2 g once daily
Comparators[a]	Pharmacological • Potassium binders ◦ SPS ◦ CPS • Diuretics ◦ Loop (furosemide) ◦ Thiazides (hydrochlorothiazide) ◦ Carbonic anhydrase inhibitors • Laxatives (e.g., lactulose) • Oral bicarbonate Stopping or reducing dose of RAASi or MRA therapy No treatment/placebo
Outcomes	Efficacy outcomes • Survival or mortality • Hyperkalemia-related hospitalization and ED visits • Quality of life[b] • MACE or MAKE • Worsening of kidney disease such as end-stage renal disease • Worsening of hyperkalemia • Maintenance or restoration of guideline-recommended maximum RAASi doses • Normalization of serum potassium (3.5 mmol/L to 5.0 mmol/L) • Recurrence of hyperkalemia • Time to requirement or need for emergency/life-threatening hyperkalemia (e.g., renal replacement therapy, IV calcium, insulin, and sodium bicarbonate) **Harms:** AEs, SAEs, WDAE, hypokalemia (tiredness, muscle weakness, or cramps), hypomagnesemia, hypercalcemia, and gastrointestinal disorders (including constipation, diarrhea, gastrointestinal ischemia, necrosis, and intestinal perforation)
Study design	For example, published and unpublished phase III and IV RCTs

ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; ED = emergency department; eGFR = estimated glomerular filtration rate; HF = heart failure; MACE = major adverse cardiovascular event; MAKE = major adverse kidney event; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; RCT = randomized controlled

trial; SAE = serious adverse event; SPS = sodium polystyrene sulfonate; WDAE = withdrawal due to adverse event.

[a]A low-potassium diet may be implemented in addition to pharmacological treatments.

[b]Outcome identified as being of particular importance to patients in the input received by CADTH from patient groups.

Description of Studies

One study, RLY5016-301 (OPAL-HK),[8] met the inclusion criteria of the systematic review (Table 7). OPAL-HK was a 2-part, single-blind, phase III study designed to assess the safety and efficacy of patiromer in 243 patients with hyperkalemia (serum potassium of 5.1 mmol/L to < 6.5 mmol/L) and CKD (eGFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2) who were receiving a stable dose of at least 1 RAASi. The study was conducted in 2 sequential parts: a 4-week part A, designed to assess the extent that patiromer reduced serum potassium in patients with varying levels of hyperkalemia, followed by an 8-week part B, designed to assess whether continuation and withdrawal of patiromer resulted in maintaining

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

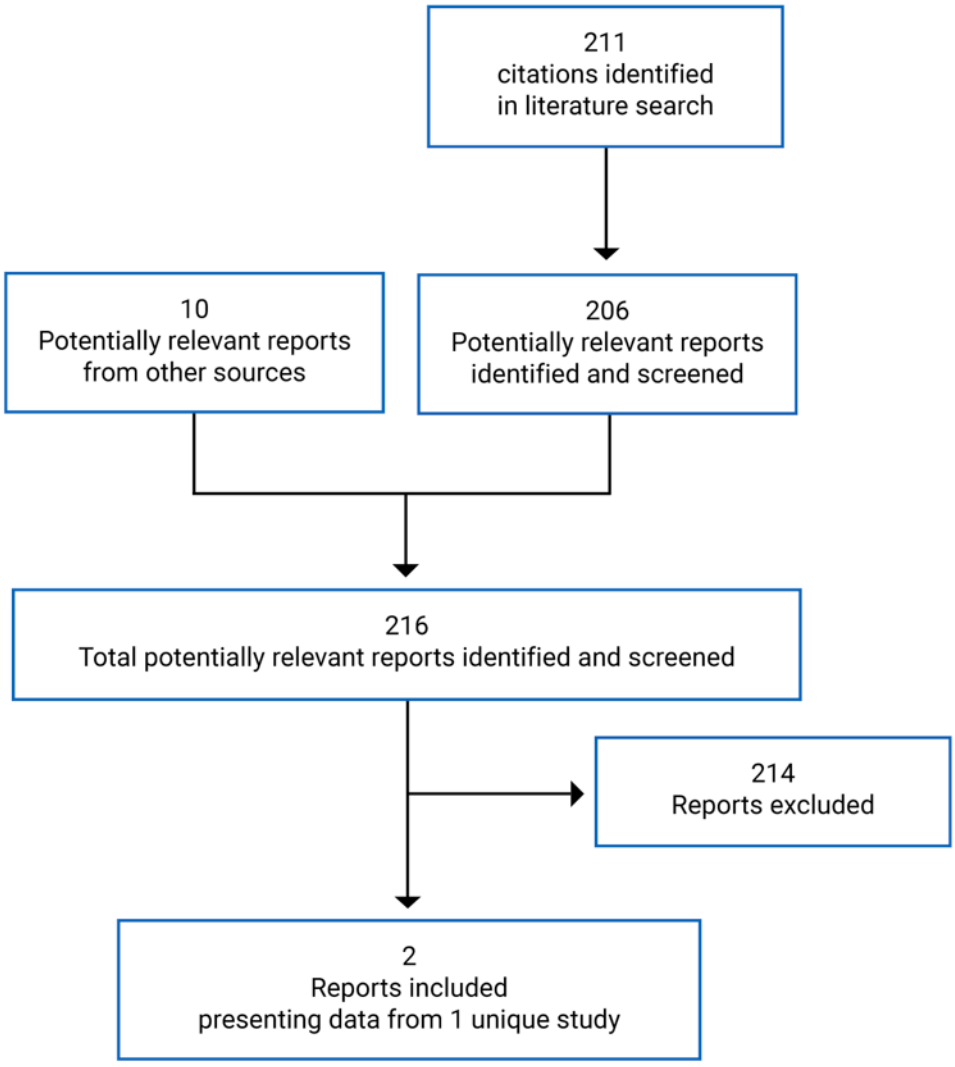


Table 8: Details of Included Studies

Detail	OPAL-HK
	Designs and populations
Study design	Two-part, single-blind, phase III study: • part A: 4-week single-blind, single-arm, oral patiromer treatment period • part B: 8-week single-blind, placebo-controlled, parallel-group, randomized withdrawal period
Objectives	**Part A** • To evaluate the efficacy and safety of patiromer for the treatment of hyperkalemia **Part B** • To evaluate the effect of withdrawing patiromer on serum potassium control • To assess whether chronic treatment with patiromer prevents the recurrence of hyperkalemia • To provide placebo-controlled safety data
Locations	Multi-centre; 71 sites, 10 countries in Europe and the US
Patient enrolment dates	February 20, 2013 (first patient enrolled) to August 6, 2013 (last patient completed last study visit)
Randomized (N)	Part A: 243 enrolled Part B: 108 randomized (107 analyzed)
Inclusion criteria	**Part A** • 18 to 80 years of age • CKD (eGFR ≥ 15 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2) • Receiving a stable dose of at least 1 RAASi (ACEi, ARB, or AA) for ≥ 28 days before screening • Hyperkalemic (screening serum potassium 5.1 mmol/L to < 6.5 mmol/L) **Part B** • Baseline serum potassium at the beginning of part A ≥ 5.5 mmol/L • Completed the 4 weeks of patiromer dosing in part A • Serum potassium at the end of part A in target range (≥ 3.8 mmol/L and < 5.1 mmol/L) • Receiving patiromer at a dose of 8.4 g/day to 50.4 g/day at the end of part A (week 4 visit) • Still receiving an RAASi at the end of part A (week 4 visit)

Detail	OPAL-HK
Exclusion criteria	**Part A** • Hyperkalemia requiring emergency intervention • Potassium-related ECG changes • Auto-immune–related CKD • type 1 diabetes or a hemoglobin A1C measurement > 10.0% in patients with T2DM • Hospitalization for hyper- or hypoglycemia (T2DM) or for acute exacerbations of HF • History of or currently diagnosed with diabetic gastroparesis or history of bariatric surgery • Screening SBP ≥ 180 mm Hg or < 110 mm Hg, or DBP ≥ 110 mm Hg or < 60 mm Hg • Symptoms associated with postural hypotension • Anuria or history of acute renal insufficiency • Confirmed diagnosis or history of renal artery stenosis • NYHA class IV HF • Uncorrected hemodynamically significant primary valvular disease • Known obstructive or restrictive cardiomyopathy or uncontrolled or hemodynamically unstable arrhythmia • Coronary artery bypass graft, percutaneous intervention, or major thoracic and cardiac surgery • Heart or kidney transplant recipient or anticipated need for transplant • Cardiovascular or cerebrovascular events • History of bowel obstruction, swallowing disorders, severe GI disorders, or major GI surgery • Any other medical condition, uncontrolled systemic disease, or serious intercurrent illness disrupting study compliance or affecting study validity • Physical and biochemical parameters: BMI ≥ 40 kg/m^2, serum magnesium < 1.4 mg/dL, liver enzymes (ALT, AST) > 3 × ULN • Active cancer, currently on cancer treatment, or history of cancer in the past 2 years • History of alcoholism or drug or chemical abuse • Use of potassium supplements, bicarbonate, or baking soda • Potassium-altering chronic medications • Current use of calcium acetate or calcium carbonate, lanthanum carbonate, sevelamer, sodium polystyrene sulfonate or calcium polystyrene sulfonate, colesevelam, colestipol, cholestyramine, drospirenone, potassium supplements, lithium, bicarbonate or baking soda, trimethoprim, tacrolimus, or cyclosporine

Detail	OPAL-HK
Drugs	
Intervention	Patiromer powder for oral suspension packaged in packets (blinded labelling); each packet contained 4.2 g of patiromer, to be consumed in the morning and evening with regular meals **Part A (4 weeks)** • Dose group 1 (screening serum potassium 5.1 mmol/L to < 5.5 mmol/L): 8.4 g/day patiromer (administered as 4.2 g b.i.d.) • Dose group 2 (screening serum potassium ≥ 5.5 mmol/L to < 6.5 mmol/L): 16.8 g/day (administered as 8.4 g b.i.d.) • Dose adjusted weekly according to part A titration algorithm (including a decrease to 0 g/day to a maximum of 50.4 g/day) to achieve target range (3.8 mmol/L to < 5.1 mmol/L) **Part B (8 weeks)** • Active dose group: Continued patiromer at the same daily dose as administered at the end of part A • Dose adjusted weekly according to part B titration algorithm (including discontinuation of dose)
Comparator(s)	**Part B only (8 weeks)** Placebo group: withdrew or discontinued patiromer treatment; placebo packaged and administered in the same manner as patiromer for blinding
Duration	
Phase	
Screening	1 day (part A only)
Single blind vs. double blind	4 weeks (part A) vs. 8 weeks (part B)
Follow-up	1 to 2 weeks; additional follow-up may be required, depending on serum potassium level
Outcomes	
Primary end point	**Part A** • Change in serum potassium from part A baseline to week 4 visit **Part B** • Change in serum potassium from part B baseline to: ◦ the part B week 4 visit (if serum potassium remained ≥ 3.8 mmol/L and < 5.5 mmol/L), or ◦ the earliest part B visit at which serum potassium was < 3.8 mmol/L or ≥ 5.5 mmol/L

Detail	OPAL-HK
Secondary and exploratory end points	**Secondary** • **Part A** ◦ Proportion of patients with serum potassium in the target range (3.8 mmol/L to < 5.1 mmol/L) at week 4 • **Part B** ◦ Proportion of patients with serum potassium ≥ 5.5 mmol/L through week 8 ◦ Proportion of patients with serum potassium ≥ 5.1 mmol/L through week 8 **Exploratory** • **Part A** ◦ Maximum reduction in serum potassium ◦ Urine albumin, urine creatinine, and urine albumin-to-creatinine ratio • **Part B** ◦ Proportion of patients requiring any adjustment of RAASi therapy by part B week 8 (i.e., down titration or discontinuation) because of hyperkalemia ◦ Proportion of patients receiving any dose of an RAASi at part B week 8 ◦ Pattern of change in both serum potassium and RAASi dosing through part B week 8
Notes	
Publications	Weir et al. (2015),[17] Pitt et al. (2015)[18]

A1C = glycated hemoglobin; AA = aldosterone antagonist; ACEi = angiotensin-converting enzyme inhibitor; ALT = alanine transaminase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; b.i.d. = twice daily; BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; ECG = electrocardiogram; GI = gastrointestinal; HF = heart failure; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor; RCT = randomized controlled trial; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; ULN = upper limit of normal.

Note: One additional report was included, the Health Canada reviewer's report.[2]

Source: OPAL-HK Clinical Study Report.[8]

control of serum potassium and recurrence of hyperkalemia, respectively. The trial design is described in detail subsequently, and in Figure 2 and Figure 3.

Part A: Part A, also known as the treatment phase, was a single-arm (non-randomized) design in which all patients received patiromer. Those meeting the screening hyperkalemia criterion received blinded patiromer treatment for 4 weeks at 2 different doses. Following screening, patients with a screening serum potassium of 5.1 mmol/L to less than 5.5 mmol/L (dose group 1) were assigned to a starting dose of 8.4 g/day patiromer, whereas those with a screening serum potassium of 5.5 mmol/L to less than 6.5 mmol/L received 16.8 g/day patiromer (dose group 2). Patients who did not complete part A or were not eligible to be randomized for part B entered a follow-up period for up to 2 weeks (longer if needed), during which no patiromer was administered and serum potassium was monitored.

Part B: Part B, also known as the withdrawal phase, was a randomized, single-blind, placebo-controlled, parallel-group period during which patients who had a baseline serum potassium of 5.5 mmol/L or greater (at the beginning of part A) and responded to patiromer treatment (achieved serum potassium between 3.8 mmol/L and less than 5.1 mmol/L at the end of part A) were randomized in a 1:1 ratio to receive 8 weeks of continued patiromer or withdrew from patiromer treatment and received placebo. Randomization was done by interactive web response system (IWRS) and was stratified to ensure equal distribution to the placebo and patiromer groups within the 4 strata formed by the combination of the following 2 baseline characteristics: T2DM (yes/no) and part A baseline serum potassium (< 5.8 mmol/L versus ≥ 5.8 mmol/L). Patients randomized to the patiromer group continued the same dose of patiromer as in part A, whereas those in the placebo group received a placebo dose equivalent to 8 g/day. Patients who completed or discontinued part B entered a 1- to 2-week follow-up period (longer if needed) similar to part A, during which they did not receive any treatment and had their serum potassium monitored.

The study was single-blinded; the investigators were aware of patients' treatment assignment while patients were blinded throughout the study. The dose of patiromer was adjusted throughout the study according to a titration algorithm, from a minimum of 0 g/day to a maximum of 50.4 g/day, with the aim of achieving serum potassium within a target range (3.8 mmol/L to 5.1 mmol/L in part A and 5.1 mmol/L to 5.5 mmol/L in part B). RAASi doses were intended to be maintained throughout the study; however, adjustments were allowed in part B to maintain serum potassium levels within 5.5 mmol/L. Details are provided in the intervention section and in the figures presented subsequently. Patients could withdraw or be withdrawn at any point from the study, based on explicit criteria (not discussed here). Notable criteria included any significant change in renal, blood pressure, diabetic, or physiologic markers, as well as major AEs or untoward events.

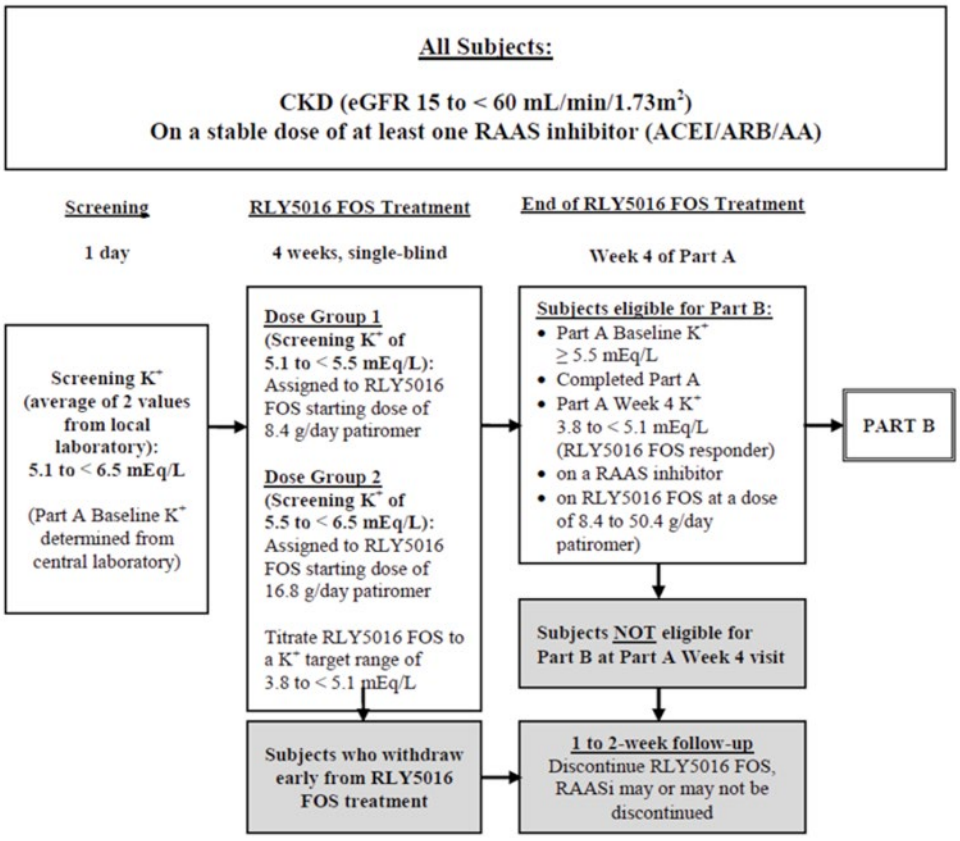
Populations

Inclusion and Exclusion Criteria

The eligibility criteria for each part of the study are listed in Table 8. For part A, adult patients (age 18 to 80) were included if they had CKD (with eGFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2), hyperkalemia (defined as 5.1 mmol/L to < 6.5 mmol/L serum potassium) and were receiving a stable dose of at least 1 RAASi (consisting of an ACEi, ARB, or aldosterone antagonist) before the start of the trial. The most notable exclusion criteria for part A included a recent history, current diagnosis, or upcoming event of any the following:

- History of or recently diagnosed clinical conditions that could interfere with disease diagnosis, or confound serum potassium results due to interfering disease pathology or medications: autoimmune-related CKD, type 1 diabetes or uncontrolled T2DM, diabetes or heart failure–related hospitalization, diabetic gastroparesis, high blood pressure, postural hypotension, anuria or acute renal insufficiency, NYHA class IV heart failure, primary valvular disease, obstructive or restrictive cardiomyopathy or uncontrolled or hemodynamically unstable arrhythmia, other cardiovascular or cerebrovascular events, or active or history of cancer or currently on cancer treatment. It should be noted that patients entering the trial could have T2DM, heart failure, and/or hypertension; however, these were not considered a requirement for inclusion.
- History of or need for major surgery: bariatric surgery, renal artery stenosis, coronary artery bypass graft, percutaneous intervention or major thoracic and cardiac surgery, or heart or kidney transplant.
- Certain physiologic parameters: BMI of 40 kg/m^2 or greater, serum magnesium of less than 1.4 mg/dL, or abnormal liver enzymes.

Figure 2: Schematic of OPAL-HK Study — Part A



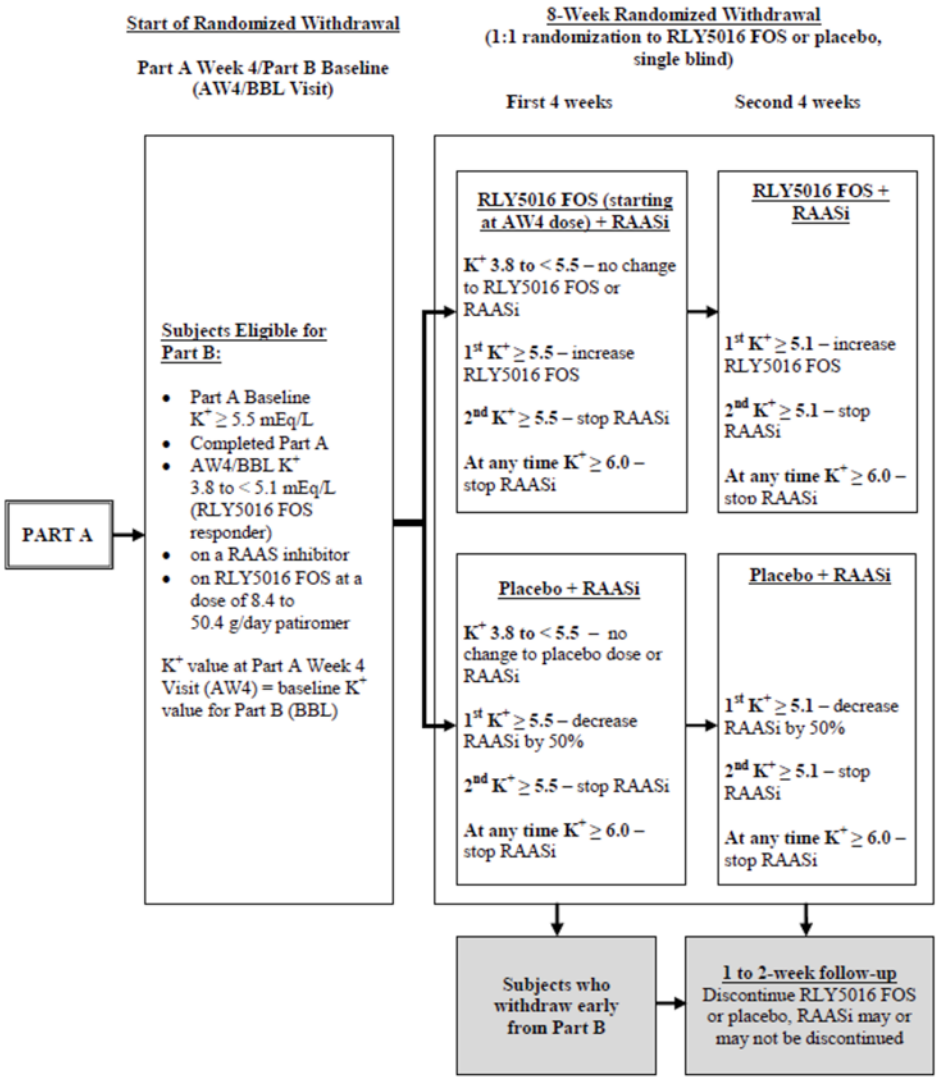
AA = aldosterone antagonist; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor; RLY5016 FOS = RLY5016 for oral suspension (patiromer).

Source: OPAL-HK Clinical Study Report.[8]

- Use of potassium-altering chronic medications or supplements or compounds: alcoholism or drug or chemical abuse, potassium supplements, lithium, bicarbonate or baking soda, calcium acetate or calcium carbonate, lanthanum carbonate, sevelamer, SPS or CPS, colesevelam, colestipol, cholestyramine, drospirenone, trimethoprim, tacrolimus, cyclosporine, or patiromer.

Patients with a baseline serum potassium of ≥ 5.5 mmol/L at the beginning of part A were allowed in part B if they met all of the following criteria at the end of part A:

Figure 3: Schematic of OPAL-HK Study — Part B



AW4 = Part A Week 4 visit; BBL = Part B Baseline visit; K^+ = potassium; RAASi = renin angiotensin aldosterone system inhibitor; RLY5016 FOS = RLY5016 for Oral Suspension

AW4 = part A week 4 visit; BBL = part B baseline visit; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor; RLY5016 FOS = RLY5016 for oral suspension (patiromer).

Source: OPAL-HK Clinical Study Report.[8]

- completed the 4-week treatment period
- achieved serum potassium in the target range (≥ 3.8 mmol/L and < 5.1 mmol/L)
- received patiromer at a dose of 8.4 g/day to 50.4 g/day
- still receiving treatment with an RAASi.

No other exclusion criteria were in place for part B of the trial.

Baseline Characteristics

Part A

Of the 243 patients enrolled into part A of the study, most (98%) were White and more than half (58%) were male, with an average age of approximately 65 years. Overall, a greater proportion of patients were assigned to dose group 2 compared with dose group 1. While patients were not randomized in part A, the baseline characteristics were largely similar in distribution between the 2 dose groups. Approximately 45% of patients had stage 3 or 4 CKD (defined as an eGFR of 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 and eGFR < 30 mL/min/1.73 m^2, respectively). Among other comorbidities, 57%, 42%, and 25% of patients had T2DM, heart failure, and myocardial infarction, respectively. Almost all patients were hypertensive. With respect to baseline medications, all patients were on RAASi therapy, as required for study inclusion, with 44% receiving the maximal dose, according to the investigator. Of the different types of RAASis patients were on, ACEis were the most frequent (70%), followed by ARBs (38%) and aldosterone antagonists (9%); 17% of patients were receiving dual RAASi blockade. Approximately three-quarters of the patients were receiving non-RAASi, non-diuretic antihypertensive medications; a greater proportion of these patients were in dose group 2, with beta blockers and calcium channel blockers being the most common. More than one-half (54%) of patients were receiving non-RAASi diuretic therapies, with identical distribution in each starting dose group. Details are provided in Table 9.

Part B

Of the 107 patients who participated in part B of the study, 54% were male and all were White; the mean age was 65 years. Demographics, medical history, and concomitant medications were mostly similar in the 2 treatment groups, considering the small sample size. Details are provided in Table 10.

Interventions

Part A

In part A of the trial, patients received blinded patiromer treatment at 2 starting doses, depending on their screening serum potassium, administered twice a day for 4 weeks, with varying volumes of water (40 mL to 120 mL, depending on dose) and regular meals (breakfast and dinner).

- Dose group 1 (serum potassium 5.1 mmol/L to < 5.5 mmol/L) received 8.4 g/day patiromer (administered as 4.2 g twice daily).
- Dose group 2 (serum potassium 5.5 mmol/L to < 6.5 mmol/L) received 16.8 g/day patiromer (administered as 8.4 g twice daily).

Dose titration protocol: The patiromer dose could be titrated weekly, with the aim of achieving serum potassium in a target range (3.8 mmol/L to 5.1 mmol/L). Titration was generally done by dose changes in increments of plus or minus 8.4 g/day. The minimum and maximum daily

Table 9: Summary of Baseline Characteristics — Part A (ITT Population)

Characteristic	OPAL-HK		
	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 92	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 151	Total 5.1 mmol/L to < 6.5 mmol/L N = 243
Demographics			
Mean age (SD), years	64.6 (11.0)	63.9 (10.2)	64.2 (10.5)
Male, n (%)	49 (53)	91 (60)	140 (58)
Race, n (%)			
White	88 (96)	151 (100)	239 (98)
Black	3 (3)	0	3 (1)
American Indian or Alaska Native	1 (1)	0	1 (< 1)
Medical history			
CKD stage,[a] n (%)			
2	6 (7)	16 (11)	22 (9)
3a	22 (24)	27 (18)	49 (20)
3b	24 (26)	39 (26)	63 (26)
4 or worse	40 (43)	69 (46)	109 (45)
Time since diagnosis (years), mean (SD)	5.2 (5.9)	3.9 (5.3)	4.4 (5.6)
Type 2 diabetes mellitus			
n (%)	52 (57)	87 (58)	139 (57)
Time since diagnosis (years), mean (SD)	14.3 (9.8)	12.6 (9.0)	13.2 (9.3)
Heart failure			
n (%)	39 (42)	63 (42)	102 (42)
Time since diagnosis (years), mean (SD)	4.7 (5.9)	2.9 (3.2)	3.6 (4.5)
NYHA class, n (%)			
Class I	7 (18)	12 (19)	19 (19)
Class II	25 (64)	41 (65)	66 (65)
Class III	7 (18)	10 (16)	17 (17)
Prior myocardial infarction			
n (%)	19 (21)	41 (27)	60 (25)
Time since diagnosis (years), mean (SD)	11.6 (10.0)	4.4 (6.8)	6.7 (8.5)
Hypertension			
n (%)	90 (98)	146 (97)	236 (97)
Time since diagnosis (years), mean (SD)	14.1 (10.2)	12.2 (8.3)	12.9 (9.1)

Characteristic	OPAL-HK		
	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 92	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 151	Total 5.1 mmol/L to < 6.5 mmol/L N = 243
Baseline medications, n (%)			
RAASi	92 (100)	151 (100)	243 (100)
ACE inhibitor	68 (74)	102 (68)	170 (70)
Angiotensin II receptor blocker	33 (36)	59 (39)	92 (38)
Aldosterone antagonist	11 (12)	11 (7)	22 (9)
On maximal dose of RAASi	42 (46)	64 (42)	106 (44)
Non-RAASi, non-diuretic antihypertensives	63 (68)	123 (81)	186 (77)
Non-RAASi diuretics	50 (54)	82 (54)	132 (54)
Magnesium	8 (9)	16 (11)	24 (10)
Insulin	20 (22)	35 (23)	55 (23)
Non-insulin antidiabetic medication	34 (37)	52 (34)	86 (35)

ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; ITT = intention to treat; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation.

[a]CKD stages: 2 = eGFR of 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2; 3a = eGFR of 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2; 3b = 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2; 4 or worse = eGFR < 30 mL/min/1.73 m^2.

Source: OPAL-HK Clinical Study Report.[8]

dose of patiromer was 0 g/day and 50.4 g/day, respectively, always administered as 2 equally divided doses.

In contrast to patiromer, the RAASi dose was to be maintained or continued throughout part A unless the following criteria were met: serum potassium level reached 6.5 mmol/L or greater, or serum potassium level was 5.1 mmol/L or greater while the patient was receiving the maximum dose of patiromer (i.e., 50.4 g/day). Dose titration for part A is further illustrated in Figure 2.

Part B

During part B of the trial, patients were randomized to receive blinded patiromer or placebo for 8 weeks, administered twice daily and with food.

- Patiromer: Continued at the same daily dose as administered at the end of part A.
- Placebo: 8 g/day, dosage split between breakfast and dinner.

Dose titration protocol: Both patiromer and RAASi doses were titrated weekly throughout the 8-week period to maintain serum potassium within 5.1 mmol/L to 5.5 mmol/L, further illustrated in Figure 3.

All RAASi medications were discontinued if a patient's serum potassium level was 6.0 mmol/L or greater. The maximum dose of patiromer was 50.4 g/day, increased in increments of 8.4 g/day. In contrast, placebo was not titrated in response to changes in serum potassium levels.

Table 10: Summary of Baseline Characteristics — Part B (ITT Population)

Characteristic	OPAL-HK	
	Placebo (N = 52)	Patiromer (N = 55)
Demographics		
Mean age (SD), years	65.0 (9.1)	65.5 (9.4)
Male, n (%)	30 (58)	28 (51)
Race, n (%)		
White	52 (100)	55 (100)
Medical history[a]		
CKD stage,[b] **n (%)**		
2	4 (8)	8 (15)
3a	11 (21)	11 (20)
3b	14 (27)	15 (27)
4 or worse	23 (44)	21 (38)
Time since diagnosis (years), mean (SD)	4.1 (5.4)	3.2 (4.3)
Type 2 diabetes mellitus		
n (%)	33 (63)	34 (62)
Time since diagnosis (years), mean (SD)	12.9 (8.2)	10.6 (6.8)
Heart failure		
n (%)	22 (42)	27 (49)
Time since diagnosis (years), mean (SD)	2.6 (2.6)	2.7 (2.8)
NYHA class, n (%)		
Class I	4 (18)	5 (19)
Class II	14 (64)	18 (67)
Class III	4 (18)	4 (15)
Prior myocardial infarction		
n (%)	14 (27)	18/ (33)
Time since diagnosis (years), mean (SD)	2.4 (2.4)	3.3 (3.0)
Hypertension		
n (%)	50 (96)	54 (98)
Time since diagnosis (years), mean (SD)	12.3 (8.0)	11.9 (6.7)
Concomitant medications, n (%)		
RAASi	52 (100)	55 (100)
ACE inhibitor	38 (73)	37 (67)

Characteristic	OPAL-HK	
	Placebo (N = 52)	Patiromer (N = 55)
Angiotensin II receptor blocker	16 (31)	24 (44)
Aldosterone antagonist	4 (8)	4 (7)
On maximal dose of RAASi	21 (40)	21 (38)
Non-RAASi, non-diuretic antihypertensives	43 (83)	44 (80)
Non-RAASi diuretics	27 (52)	28 (51)
Magnesium	6 (12)	9 (16)
Insulin	15 (29)	13 (24)
Non-insulin antidiabetic medication	20 (38)	22 (40)

ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; ITT = intention to treat; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation.

[a]Recorded at part A baseline for the patients who participated in part B.

[b]CKD stages: 2 = eGFR of 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2; 3a = eGFR of 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2; 3b = eGFR of 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2; 4 or worse = eGFR of < 30 mL/min/1.73 m^2.

Source: OPAL-HK Clinical Study Report.[8]

It should be noted that patients could receive patiromer for a maximum of 12 weeks (part A and B), whereas placebo was administered for up to 8 weeks. Both patiromer and placebo were available as powdered oral suspension and were packaged and dispensed in an identical manner.

Concomitant Medications

In general, patients were allowed to continue the regular doses of their usual medications, as long as none of these drugs were listed as exclusionary medication for eligibility. Permitted antihypertensive medications included non-RAASi antihypertensive drugs that did not affect serum potassium levels (e.g., calcium channel blocker, alpha blocker, or alpha-2 agonist). No new RAASi medications were to be initiated during the study and doses of RAASi medications were not changed unless the patient became hyperkalemic and required dose titration according to pre-specified protocol. Notable medications for heart failure included aldosterone antagonists (e.g., spironolactone or eplerenone), thiazide and loop diuretics, beta-adrenergic blockers, and digitalis glycosides. Other notable medications permitted included those for T2DM, stroke risk, gout, and dyslipidemia.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 11. These end points are further summarized in the table.

Efficacy End Points

Serum potassium values were assessed by both central and local laboratories and analyzed at all weekly study visits. Notably, local laboratory values were used for screening criteria and dose titration, while central laboratory values were used to report efficacy data (unless otherwise reported). Special procedures were in place for preventing, identifying, and handling hemolyzed blood samples to prevent a spuriously high serum potassium value. These

procedures included testing for hemolysis of each blood sample received for potassium analysis by the central laboratory. A number of exploratory efficacy outcomes were measured, based on aspects of RAASi dosing and dose adjustments.

Primary Efficacy End Points

In both part A and B, the primary efficacy end point was the mean change in serum potassium at week 4 from the respective baseline. For part A, the sponsor indicated that to satisfy the FDA's established criteria, serum potassium should be reduced by 0.7 mmol/L or greater from baseline (with a significant reduction, $P < 0.05$). The selection of 0.7 mmol/L was based on doubling of 0.36 mmol/L, which was the estimated maximum change in serum potassium from baseline that could result from undetected hemolysis in serum samples.[2]

Secondary Efficacy End Points

The secondary efficacy end points in both parts of the study were similar in nature: Part A measured the proportion of patients within the target serum potassium range of 3.8 mmol/L to less than 5.1 mmol/L at week 4, whereas part B measured the proportion of patients outside of the target serum potassium range of 5.1 mmol/L or greater and 5.5 mmol/L or greater at week 8.

Table 11: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	OPAL-HK
Part A	
Primary	Change from part A baseline in serum potassium at week 4
Secondary	Proportion of patients with serum potassium ≥ 3.8 mmol/L to < 5.1 mmol/L at week 4
Exploratory	Maximum reduction of serum potassium (reported as proportion of patients with any increase, no change, > 0.0 mmol/L to < 0.3 mmol/L, 0.3 mmol/L to 0.5 mmol/L, and > 0.5 mmol/L of reduction) Patiromer titrations: Overall, increases, decreases (reported as proportion by cumulative number of titrations through week 4, distribution of the cumulative number of titrations through week 4, number of titrations by time point in part A)
Part B	
Primary	Change in serum potassium from part B baseline to week 4 or earliest visit with first serum potassium value out of the target range (≥ 3.8 mmol/L and < 5.5 mmol/L)
Secondary	Proportion of patients throughout week 8 (part B) with serum potassium ≥ 5.1 mmol/L or ≥ 5.5 mmol/L
Exploratory	Time to the first occurrence of serum potassium ≥ 5.5 mmol/L and ≥ 5.1 mmol/L Time to recurrent hyperkalemia (first occurrence of a serum potassium ≥ 5.5 mmol/L during weeks 1 to 4 of part B or ≥ 5.1 mmol/L during weeks 5 to 8 of part B) Proportions of patients who required protocol-specified interventions for management of recurrent hyperkalemia Proportion of patients at part B week 8: Taking any RAASi dose or taking a maximum RAASi dose Proportion of patients with serum potassium values in range for each part B visit

RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: OPAL-HK Clinical Study Report.[8]

Exploratory Efficacy End Points

Exploratory efficacy end points in part B included the proportion of patients who required protocol-specified management of recurrent hyperkalemia (i.e., RAASi dose reduction or discontinuation in the placebo group; patiromer dose increase or RAASi discontinuation in the patiromer group).

Safety End Points

Safety was assessed by a number of end points using standard definitions based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance. An AE was defined as onset or worsening of any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study treatments. AEs were graded as mild, moderate, or severe. An SAE was any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event that jeopardized the patient or required medical or surgical intervention. In addition, the protocol-defined AEs of interest included the following: hypokalemia (serum potassium < 3.5 mmol/L), serum potassium of 5.5 mmol/L or greater, GI-related AEs, and changes in serum calcium, magnesium, and fluoride.

Statistical Analysis

Analyses of Efficacy End Points

Part A

For the primary efficacy end point, the mean change in serum potassium and 95% CI was estimated using a longitudinal repeated measures model of the centrally measured, weekly post-baseline values of serum potassium from week 1 through week 4. An unstructured covariance structure was used to model within-patient correlations. The model included the following covariates: time (defined by weekly time points), presence of heart failure at baseline and presence of T2DM at baseline as binary covariates, and part A baseline serum potassium (central laboratory) as continuous covariate.

For the secondary efficacy end point, stratified estimates of the proportion, standard error and 95% CI were calculated with stratification by the following binary variables: heart failure at baseline (yes/no), T2DM at baseline (yes/no) and part A baseline serum potassium level (< 5.5 mmol/L versus ≥ 5.5 mmol/L). Exploratory efficacy outcomes were summarized descriptively without formal statistical testing.

A number of pre-specified subgroups were summarized descriptively for the part A primary and secondary efficacy end points, of which the following ones are relevant and included for this review: presence or absence of T2DM or heart failure, serum potassium (< 5.5 mmol/L, ≥ 5.5 mmol/L) at part A baseline, and whether the patient was on a maximal RAASi medication dose at the part A baseline according to the investigator's assessment. Subgroup analyses were analogous to those used in the overall analysis of the corresponding end point, without adjustment for multiplicity, and appropriate statistical analyses were completed through the use of interaction effects in the models.

Part B

For the primary efficacy end point of part B, the 2 treatment groups were compared using an analysis of variance (ANOVA) of the rank-transformed data that included factors

corresponding to the 4 randomization strata at part A baseline: serum potassium (< 5.8 mmol/L, ≥ 5.8 mmol/L), and presence of T2DM (yes/no). The rank-transformation approach for the ANOVA model was applied because the post-baseline values could come from different post-baseline time points, as they were affected by clinical intervention (e.g., if a patient's serum potassium value was outside the range of 3.8 mmol/L to < 5.5 mmol/L) and, therefore, could not be assumed to be samples from 1 common distribution. This approach accounted for patients with serum potassium values outside the range before part B week 4 by using the last observed rank carried forward method. The mean difference in ranks estimated by ANOVA was compared using a 2-sided t-test at a type I error rate of 0.05. A Hodges-Lehmann estimator was used for the between-group difference in median change in serum potassium, which was calculated along with its 95% CI. The estimated change from baseline value for a patient used in the calculation of between-group difference in median change could differ from the observed change for the patients defined by the primary efficacy end point.

For each of the 2 secondary efficacy end points, the proportions in the 2 treatment groups were compared using a Mantel-Haenszel test stratified by the 4 randomization strata; a Hochberg correction was used in assessing these 2 end points to ensure an overall type I error rate of 0.05. Exploratory efficacy outcomes were summarized descriptively without formal statistical testing.

The part B primary and secondary efficacy end points were summarized descriptively by the same subgroups listed previously and analyzed using the same method used in the overall analysis of the corresponding end point.

Handling of Missing Data

Part A

No multiple imputation was used in the analysis of the part A primary efficacy end point other than the following scenario. In the event the central laboratory serum potassium value was missing at a given visit and the corresponding local laboratory serum potassium value was available, an imputed central laboratory value was computed for analysis using a regression model that predicted the central serum potassium value from the local laboratory value. The variables selected for this regression model were central laboratory location (US versus Europe) and local laboratory measurement of serum potassium, using interim laboratory data. The parameter estimates for the regression model were calculated using the final laboratory data.

For the secondary efficacy outcome, multiple imputation was used for patients who completed the week 4 visit of part A but both the central and local laboratory serum potassium data were missing data on that visit.

Part B

For the primary efficacy end point, depending on the reason for missing data, the following approaches of handling missing data were used: imputation using a regression analysis, imputation based on the action taken on the patiromer and RAASi doses, or multiple imputation. Imputation using a regression model was done in the same manner as the part A primary efficacy end point described previously.

Sensitivity Analyses

The following sensitivity analyses were performed to assess the robustness of the efficacy results by repeating the primary efficacy analysis of both part A and B after excluding patients meeting each of the following criteria:

- **Baseline serum potassium not meeting part A or B entry criterion:** Entry into part A of the study required a serum potassium of greater than 5.1 mmol/L, measured at baseline using the average of 2 values from the local laboratory. However, a number of patients had a serum potassium value of less than 5.1 mmol/L according to central laboratory measurement, i.e., they were not considered hyperkalemic. This sensitivity analysis included 216 (91%) of the 237 patients who were included in the primary analysis. Similarly, to be eligible for part B, a patient's local laboratory serum potassium had to be in the target range (3.8 mmol/L to < 5.1 mmol/L) at the end of part A. Two separate sensitivity analyses were performed excluding those with a serum potassium of less than 3.8 mmol/L and those with a level of 5.1 mmol/L or greater, which resulted in the inclusion of 105 (98%) and 103 (96%) of the 107 patients in the part B primary efficacy analysis, respectively.
- **RAASi medication adjusted without meeting the protocol-specified titration criteria:** This included 232 (98%) of the 237 patients who were included in the part A primary analysis, and 101 (94%) of the 107 patients in the part B primary analysis.
- **Compliance with study drug (< 80% or > 120%):** The analysis included 235 (99%) of the 237 patients who were included in the part A primary analysis and included 105 (98%) of the 107 patients in the part B primary efficacy analysis.
- **Patients enrolled at site 1907:** This analysis was done to exclude patients from site 1907 to assess if a sample processing error made any difference to the efficacy results. For the part A and part B primary efficacy end points, the analyses were rerun with 226 (95%) of the 237 patients in part A and 97 (91%) of the 107 patients in part B.
- **Patients with important protocol deviations:** This was the per-protocol analysis. It included 222 (94%) of the 237 patients included in the part A primary analysis and 105 (98%) of the 107 patients in the part B primary efficacy end point analysis.
- **Inclusion of all patients in the part A ITT population:** This analysis used a last observation carried forward approach to include all 243 patients in the part A ITT population, including those with no post–part A baseline serum potassium measurements.

Sample Size

The sample size of the study was planned to have at least 90% statistical power to detect a difference between patiromer and placebo with respect to the primary efficacy outcome in part B. Assuming a difference of 0.48 mmol/L between the patiromer and placebo groups in the mean change in serum potassium from part B baseline to part B week 4 (with an SD of 0.40 mmol/L in both groups), it was estimated that a sample size of 40 patients in each group was needed to provide more than 90% power. Approximately 240 patients were planned to be enrolled in part A to ensure at least 40 patients per group in part B. With 240 patients enrolled, part A was estimated to have more than 99% power at a 5% significance level to detect a mean change from baseline in serum potassium of 0.3 mmol/L or greater (with an SD of 0.55 mmol/L). The estimates were based on data from patients receiving patiromer in the AMETHYST-DN trial (Study 205). The power for a subgroup size of 35 was approximately 90%.

Safety Analyses

AEs were summarized descriptively for both parts of the study and included the incidence of AEs with onset during part A and during part B separately, as well as the incidence of AEs

reported at any time during the study for those patients who continued through the end of part B. AEs were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) (version 12.0) and summarized by system organ class and preferred term. Standardized MedDRA Queries were used to identify and summarize several notable safety events, including GI events.

Analysis Populations

All baseline, exposure, and efficacy results were measured in the ITT population, although the definition varied slightly between part A and B. For part A, the ITT population was originally

Table 12: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors/covariates/ stratification	Sensitivity analyses
Primary efficacy end point			
Part A: Mean change at week 4 in serum potassium from (part A) baseline	Longitudinal repeated measures model with unstructured covariance structure was used to model within-patient correlations	Binary: Time (defined by weekly time points), presence of HF at baseline and presence of T2DM at baseline Continuous: Baseline serum potassium	Baseline serum potassium not meeting entry criteria RAASi medication adjusted without meeting the protocol-specified titration criteria Compliance with study drug (< 80% or > 120%) Patients enrolled at site 1907 Patients with important protocol deviations Inclusion of all patients in the part A ITT population
Part B: Mean change in serum potassium from (part B) baseline to week 4 or earliest visit with first serum potassium value out of the target range (≥ 3.8 mmol/L and < 5.5 mmol/L)	ANOVA model with rank-transformed data	Stratified by serum potassium (< 5.8 mmol/L, ≥ 5.8 mmol/L), and presence of T2DM (yes/ no)	Same as for part A (excluding the last one)
Secondary efficacy end point			
Part A: Proportion of patients with serum potassium ≥ 3.8 mmol/L to < 5.1 mmol/L at week 4	Proportion, SE, and 95% CI calculated; no analysis done	Stratified by: HF at baseline (yes/no), T2DM at baseline (yes/no), and part A baseline serum potassium level (< 5.5 mmol/L vs. ≥ 5.5 mmol/L)	None
Part B: Proportion of patients throughout week 8 with serum potassium ≥ 5.1 mmol/L or ≥ 5.5 mmol/L	Proportions compared using a Mantel-Haenszel test	Stratified by: HF at baseline (yes/no), T2DM at baseline (yes/no), and part A baseline serum potassium level (< 5.5 mmol/L vs. ≥ 5.5 mmol/L)	None

ANOVA = analysis of variance; CI = confidence interval; HF = heart failure; ITT = intention to treat; RAASi = renin-angiotensin-aldosterone system inhibitor; SE = standard error; T2DM = type 2 diabetes mellitus.

Source: OPAL-HK Clinical Study Report.[8]

defined as all patients who met all eligibility criteria for part A and received at least 1 dose of patiromer. However, the definition was later changed to only include patients who received at least 1 dose of patiromer. For part B, the ITT population was defined as patients who met all eligibility criteria for part B and were randomized to either the patiromer or placebo group.

Some efficacy analyses were repeated based on per-protocol populations for part A and part B. The per-protocol populations comprised those patients in the respective ITT population who were compliant (i.e., took 80% to 120% of the dispensed dose) and did not have any important protocol deviations.

All safety data were reported in the safety population, defined as all enrolled (for part A) or randomized (for part B) patients who received at least 1 dose of the study drug for that part of the trial.

Results

Patient Disposition

Results were provided for the ITT population of the respective parts.

Part A

A total of 395 patients were assessed for eligibility in the trial, of which 38% failed to meet the screening criteria, leaving 243 patients enrolled in part A of the trial. Notably, more patients were assigned to dose group 2, since they had a higher baseline serum potassium. Approximately 10% of patients did not complete the first part of the trial, primarily due to AEs. The frequency of study completion and discontinuation were similar in both dose groups.

At the end of part A, a total of 136 patients did not participate in part B and entered the part A follow-up, during which they did not receive further patiromer treatment. Of these, 24 patients withdrew early from part A, 108 patients completed part A but were not eligible for part B, and 3 patients elected not to continue into part B despite completing part A and being eligible for part B. A total of 121 (89%) of these 136 patients completed the part A follow-up. At the end of part A, 45% patients met the eligibility criteria for part B, and 45% did not. The primary reason for not meeting the part B eligibility criteria was not having a serum potassium of 5.5 mmol/L or greater at part A baseline. Details are provided in Table 13.

Part B

A total of 108 patients were randomized into part B of the trial (Table 14). Of these, 4 times more patients were from dose group 2 compared with dose group 1, accounting for the higher baseline serum potassium in the former group, which was a key criterion for entering part B. Notably, 1 patient was randomized in error into part B but did not actually participate.

Of the 107 patients who participated in part B, approximately 90% completed up to week 4, with similar proportions in both groups. Notably, a smaller proportion of patients completed part B up to week 8, particularly in the placebo group. Having high serum potassium was the primary reason for discontinuation, especially in the placebo group.

Exposure to Study Treatments

In both parts of the trial, treatment compliance was high; the mean overall percentage of patients who adhered to treatment was 99.4% and 100.7% in part A and B, respectively (calculated as a percentage of the total dose by the expected dose; data not presented).

Table 13: Disposition — Part A (ITT Population)

Disposition (part A)	OPAL-HK		
	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 92	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 151	Total 5.1 mmol/L to < 6.5 mmol/L N = 243
Screened, N	395		
Screening failure, N (%)	152 (38)		
Enrolled in part A, N (%)	243 (62%)		
Part A treatment phase			
Treated, N (%)	92 (100)	151 (100)	243 (100)
Completed, n (%)	85 (92)	134 (89)	219 (90)
Did not complete part A, n (%)	7 (8)	17 (11)	24 (10)
Adverse event	2 (2)	8 (5)	10 (4)
Withdrawal by patient	2 (2)	3 (2)	5 (2)
Met protocol-specified withdrawal criteria (high serum K^+ results)	1 (1)	2 (1)	3 (1)
Met protocol-specified withdrawal criteria (eGFR decrease to < 10 mL/min/1.73 m^2 or need for dialysis)	2 (2)	0	2 (1)
Protocol violation	0	2 (1)	2 (1)
Met protocol-specified withdrawal criteria (low serum K^+ results)	0	1 (1)	1 (< 1)
Non-compliance with study drug	0	1 (1)	1 (< 1)
Eligible for part B, n (%)	16 (17)	94 (62)	110 (45)
Not eligible for part B, n (%)	69 (75)	40 (26)	109 (45)
Central laboratory serum K^+ not ≥ 5.5 mmol/L at ABL	64 (70)	33 (22)	97 (40)
AW4 (BBL) local laboratory serum K^+ not in normal range of 3.8 mmol/L to < 5.1 mmol/L	11 (12)	11 (7)	22 (9)
Not taking RAASi	2 (2)	0	2 (1)
Not on 8.4 g/day to 50.4 g/day dose of patiromer	5 (5)	2 (1)	7 (3)
2-week follow-up after part A treatment phase, n (%)			
Follow-up visits	77 (84)	58 (38)	135 (56)
Completed follow-up	72 (78)	49 (32)	121 (50)
Did not complete follow-up	5 (5)	9 (6)	14 (6)
Randomized into part B, n (%)	15 (16)	93 (62)	108 (44)
Eligible, received study medication and included in the ITT population	15 (16)	92 (61)	107 (44)

Disposition (part A)	OPAL-HK		
	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 92	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 151	Total 5.1 mmol/L to < 6.5 mmol/L N = 243
Not eligible, did not receive study medication and not included in the ITT population[a]	0	1 (1)	1 (< 1)
ITT population, N (%)			
Included in the primary efficacy analysis[b]/mITT	90 (98)	147 (97)	237 (98)
Included in all other efficacy analyses[c]	92 (100)	151 (100)	243 (100)
Safety population,[d] N (%)	92 (100)	151 (100)	243 (100)
Per-protocol populations, N (%)	84 (91)	139 (92)	223 (92)
Per-protocol populations for the primary efficacy analysis, N (%)	82 (89)	138 (91)	220 (91)

ABL = part A baseline; AW4 = part A week 4; BBL = part B baseline; eGFR = estimated glomerular filtration rate; (m)ITT = (modified) intention to treat; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.

[a]One patient in dose group 2 was not eligible for part B but was randomized in error. This error was identified before the patient received any randomized treatment and the patient subsequently entered into the part A follow-up. Because this patient was not eligible for part B, did not receive any randomized treatment, and had no part B assessment beyond AW4 (BBL), this patient was not included in the ITT population of part B.

[b]The mITT population consisted of 237 out of the 243 patients in the ITT population. These were the patients enrolled into the part A treatment phase who received at least 1 dose of patiromer and had either a central or local laboratory serum potassium result at ABL and at least 1 post-baseline weekly visit (i.e., part A week 1 or later). Six of the 243 patients in the ITT set had no post-baseline serum potassium because of early withdrawal from part A.

[c]Patients enrolled into the part A treatment phase who received at least 1 dose of patiromer and had either a central or local laboratory serum potassium result at ABL and at least 1 post-baseline weekly visit (i.e., part A week 1 or later).

[d]Patients enrolled into the part A treatment phase who received at least 1 dose of patiromer.

Source: OPAL-HK Clinical Study Report.[8]

In part A, both dose groups received an average of 27 days of patiromer treatment, with a mean daily dose of patiromer (i.e., resulting from titrations) of 12.8 g in group 1, and 21.4 g in group 2. Among the patients who received patiromer, 60% reported at least 1 dose titration (Table 15). Notably, dose increases were reported by a larger proportion of patients than were dose decreases (56% versus 9% overall; data not presented).

For patients randomized to patiromer during part B, the mean daily dose was 21.2 g, with an average of 51 days of treatment. In contrast to part A, the majority of patients (85%) did not require any dose titration (Table 16). Notably, dose titrations resulting in a dose decrease were not permitted in part B.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported subsequently. All efficacy results were reported in the ITT population of the respective parts. Notably, the primary analysis consisted of 237 patients, as 6 of the 243 patients in the ITT set had no post-baseline serum potassium because of early withdrawal from part A. However, sensitivity analysis using imputed serum potassium values showed no difference in results. Unless otherwise mentioned, all results on serum potassium were based on central laboratory measurements. See Appendix 3 for detailed efficacy data.

Change in Serum Potassium

PART A

Results for the primary and secondary efficacy end points for part A are provided in Table 17.

The primary efficacy outcomes (i.e., the mean change [standard error]) from baseline in serum potassium at week 4 in dose groups 1 and 2 were −0.65 mmol/L (0.05 mmol/L) and −1.23 mmol/L (0.04 mmol/L), respectively. Overall, there was a statistically significant mean decrease of 1.01 mmol/L (0.03 mmol/L) in serum potassium from baseline through week 4 ($P < 0.001$). The primary efficacy end point therefore met the threshold value for serum potassium change from baseline set by the FDA to be considered pivotal (≥ 0.7 mmol/L with $P < 0.05$).[2] Notably, 10% of patients did not complete part A. All sensitivity analyses (as

Table 14: Disposition — Part B (ITT Population)

Disposition (part B)	OPAL-HK	
	Placebo (N = 52)	Patiromer (N = 55)
Part B randomized withdrawal phase		
Remained on treatment through part B week 4, n (%)	45 (87)	50 (91)
Discontinued treatment before part B week 4, n (%)	7 (13)	5 (9)
Completed part B, n (%)	30 (58)	45 (82)
Did not complete part B, n (%)	22 (42)	10 (18)
Met protocol-specified withdrawal criteria (high serum potassium results)	14 (27)	2 (4)
Met protocol-specified withdrawal criteria (low serum potassium results)	1 (2)	2 (4)
Met protocol-specified withdrawal criteria (serum potassium results)	2 (4)	1 (2)
Adverse event	1 (2)	1 (2)
Met protocol-specified withdrawal criteria (eGFR decrease to < 10 mL/min/1.73 m^2 or need for dialysis)	1 (2)	1 (2)
Physician decision	1 (2)	1 (2)
Death	1 (2)	0
Lost to follow-up	0	1 (2)
Non-compliance with study drug	0	1 (2)
Withdrawal by patient	1 (2)	0
2-week follow-up after part B randomized withdrawal phase, n (%)		
Completed follow-up	45 (87)	51 (93)
Did not complete follow-up	7 (13)	4 (7)
ITT population, N (%)	52 (100)	55 (100)
Safety population, N (%)	52 (100)	55 (100)
Per-protocol populations, N (%)	49 (94)	54 (98)

eGFR = estimated glomerular filtration rate; ITT = intention to treat.

Source: OPAL-HK Clinical Study Report.[8]

described previously), showed results similar to the primary analysis, demonstrating the robustness of the findings in the primary analysis (data not presented).

It should be noted that change from baseline in serum potassium was not tested statistically for the 2 dose groups; instead, they were collapsed into 1 for statistical comparison as per design (single arm). It is therefore unclear if patiromer had a statistically significant potassium-lowering effect among patients on the lower end of mild hyperkalemia (5.1 mmol/L to < 5.5 mmol/L) as it did among those on the higher end of mild hyperkalemia (≥ 5.5 mmol/L). Importantly, serum potassium in dose group 1 was reduced by 0.65 mmol/L from baseline, which did not meet the pre-specified cut-off value of 0.7 mmol/L or greater needed to consider a clinically meaningful effect, as set by the FDA.

Table 15: Patiromer Exposure — Part A (ITT Population)

Patiromer exposure (part A)	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 92	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 151	Total 5.1 mmol/L to < 6.5 mmol/L N = 243
Duration (days), mean (SD)	27.0 (6.5)	27.0 (6.2)	27.0 (6.3)
Total patiromer received (g), mean (SD)	346.8 (171.8)	572.3 (194.2)	486.9 (215.6)
Patiromer daily dose (g/day), mean (SD)	12.8 (5.4)	21.4 (5.1)	18.2 (6.6)
Number of dose titrations per patient, mean (SD)	0.8 (0.9)	0.9 (0.8)	0.9 (0.9)
Patients with any patiromer dose titration, n (%)			
0	38 (41)	58 (38)	96 (40)
1	34 (37)	57 (38)	91 (37)
2	16 (17)	31 (21)	47 (19)
> 2	4 (4)	5 (3)	9 (4)

ITT = intention to treat; SD = standard deviation.
Source: OPAL-HK Clinical Study Report.[8]

Table 16: Exposure to Treatment — Part B (ITT Population)

Patiromer exposure (part B)	Placebo (N = 52)	Patiromer (N = 55)
Duration (days), mean (SD)	46.3 (16.0)	51.4 (13.5)
Total treatment received (g), mean (SD)	362.3 (127.8)	1,065.3 (502.1)
Treatment daily dose (g/day), mean (SD)	7.9 (0.2)	21.2 (8.1)
Patients with any patiromer dose titration, n (%)		
0	—	47 (85)
1	—	8 (15)

ITT = intention to treat; SD = standard deviation.
Source: OPAL-HK Clinical Study Report.[8]

The secondary end point, i.e., the proportion of patients with a serum potassium level within the target range at week 4, was 76% overall (both groups), with similar percentages in each dose group (74% and 77% in dose group 1 and 2, respectively). Results were stratified by heart failure, T2DM, and the part A baseline serum potassium value (< 5.5 mmol/L or ≥ 5.5 mmol/L). Notably, these analyses were not controlled for multiplicity and are at risk of type I error; they should be viewed as supportive evidence in the overall assessment of patiromer.

Figure 4 shows the modelled mean serum potassium levels over time in part A for each dose group and overall. There was a substantial reduction in serum potassium by day 3 overall, from 5.58 mmol/L at baseline to 5.14 mmol/L, which was just above the upper end of the target range for serum potassium in part A (5.1 mmol/L). Reduction in serum potassium levels continued through week 3, with no appreciable difference following week 3. Dose group 2 had a greater reduction in mean serum potassium levels over time, after starting with a higher baseline serum potassium level (as per definition).

Table 17: Outcomes on Serum Potassium — Part A (mITT Population)

Outcomes	Dose group 1 5.1 mmol/L to < 5.5 mmol/L (N = 90)	Dose group 2 5.5 mmol/L to < 6.5 mmol/L (N = 147)	Total 5.1 mmol/L to < 6.5 mmol/L (N = 237)
Primary efficacy end point: change in serum K^+, mmol/L			
Part A baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	
Part A week 4			
Mean ± SE	−0.65 ± 0.049	−1.23 ± 0.040	−1.01 ± 0.031
95% CI	−0.74 to −0.55	−1.31 to −1.16	−1.07 to −0.95
P value	—	—	< 0.001
Secondary efficacy end point: proportion of patients with serum K^+ in the target range (3.8 mmol/L to < 5.1 mmol/L) at week 4			
Stratified percentage, % (95% CI)			
Success	74 (65 to 82)	77 (70 to 83)	76 (70 to 81)
Failure: Either reason[a]	26 (18 to 35)	23 (17 to 30)	24 (19 to 30)
Unstratified (raw) percentage, n (%)			
Success	68 (74)	116 (77)	184 (76)
Failure: Either reason	24 (26)	35 (23)	59 (24)
Did not complete part A	7 (8)	17 (11)	24 (10)
Part A serum K^+ < 3.8 mmol/L or ≥ 5.1 mmol/L	17 (18)	18 (12)	35 (14)
< 3.8 mmol/L	1 (1)	7 (5)	8 (3)
≥ 5.1 mmol/L	16 (17)	11 (7)	27 (11)

CI = confidence interval; ITT = intention to treat; K^+ = potassium; mITT = modified intention to treat; SD = standard deviation; SE = standard error.

Note: The mITT population consisted of 237 out of the 243 patients in the ITT population. Patients enrolled into the part A treatment phase received at least 1 dose of patiromer and had either a central or local laboratory serum K^+ result at part A baseline and at least 1 post-baseline weekly visit (i.e., part A week 1 or later). Six of the 243 patients in the ITT set had no post-baseline serum K^+ because of early withdrawal from part A.

[a]Patients could fail either by not completing part A or having a part A serum K^+ not in the target range (i.e., < 3.8 mmol/L or ≥ 5.1 mmol/L).

Source: OPAL-HK Clinical Study Report.[8]

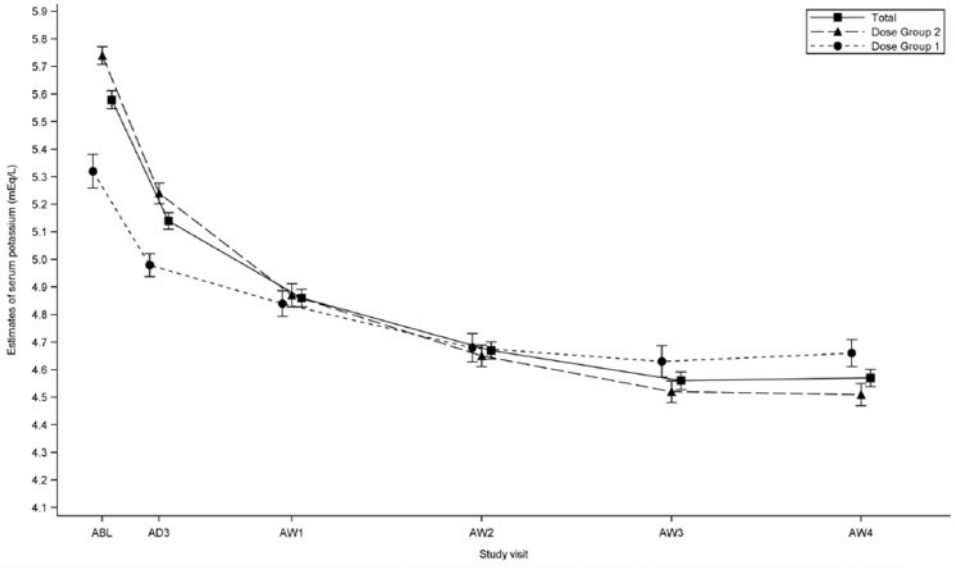
Subgroup Analyses of Efficacy: The part A primary and secondary end points were summarized by the following subgroups: T2DM, heart failure, part A baseline serum potassium (< 5.5 mmol/L, ≥ 5.5 mmol/L) and whether the patient was on a maximal RAASi medication dose. Results are provided in Appendix 3 (Table 30 and Table 31). Across all subgroups, the direction of the effect was the same as the overall analysis, with generally no statistical difference or interaction noted between the subgroups. The only subgroup showing a differential response was the part A baseline serum potassium level (interaction P < 0.001), which was observed for the primary efficacy outcome only (Table 30).

Exploratory Analyses of Efficacy: The only exploratory end point relevant for this review, the maximum reduction from baseline in serum potassium during part A, was determined for 234 patients who had a central laboratory serum potassium value at baseline and at least 1 post-baseline visit. The maximum reduction was greater than 0.5 mmol/L for 88% (205 of 234) of patients, 0.3 mmol/L to 0.5 mmol/L for 8% (19 of 234) of patients, and less than 0.3 mmol/L for 3% (6 of 234) of patients (data not presented).

PART B

The primary efficacy end point was the change in serum potassium from part B baseline through week 4, or the earliest time point at which serum potassium was within the target range. At part B baseline, both the placebo and patiromer groups had similar distributions of serum potassium (4.45 mmol/L and 4.49 mmol/L, respectively). At the end of week 4 (time point for part B primary efficacy end point), the patients in the placebo group had a median increase of 0.72 mmol/L in serum potassium; the patiromer group had no median change.

Figure 4: Change From Baseline in Serum Potassium Over Time — Part A (mITT Population)



Abbreviations: ABL = Part A Baseline; AD3 = Part A Day 3; AW1 = Part A Week 1; AW2 = Part A Week 2; AW3 = Part A Week 3; AW4 = Part A Week 4; ANOVA = analysis of variance; ITT = intent-to-treat; RLY5016 FOS = RLY5016 for Oral Suspension; SE = standard error
Estimates of mean and SE come from an ANOVA model using data from subjects in the ITT population of Part A who have either a local or central laboratory serum potassium result at baseline and at least one weekly post-baseline visit. Estimates are staggered in this figure to make them more legible.
*These estimates exclude six subjects who had no result collected after Part A Day 3.

ABL = part A baseline; AD3 = part A day 3; AW1 = part A week 1; AW2 = part A week 2; AW3 = part A week 3; AW4 = part A week 4.

Source: OPAL-HK Clinical Study Report.[8]

The estimated between-group difference in median change was statistically significant (0.72 mmol/L; P < 0.001) (Table 18). As noted earlier in patient disposition (Table 14), of the 107 patients who participated in part B, 7 patients in the placebo group and 5 patients in the patiromer group discontinued before week 4. Four of these patients had their serum potassium values imputed (1 in the placebo group and 3 in the patiromer group). A number of sensitivity analyses were conducted to assess the robustness of the primary efficacy result (as described previously); the results were consistent with findings from the primary efficacy analysis (data not presented).

The secondary end points for part B were the proportions of patients with a serum potassium of 5.1 mmol/L or greater and 5.5 mmol/L or greater at any point post-baseline through week 8. Stratified and raw percentages are provided in Table 18. A statistically significantly greater proportion of patients in the placebo group had a serum potassium level outside the target range compared with patiromer: 91% versus 43% for 5.1 mmol/L or greater, and 60% versus 15% for 5.5 mmol/L or greater. These 2 end points were estimated using both observed central laboratory serum potassium values and values imputed using local laboratory results and/or multiple imputation.

Subgroup Analyses of Efficacy: The part B primary and secondary end points were summarized by the subgroups described previously. Results were similar to the respective primary and secondary end points. None of the subgroups showed any difference in the direction of effect for either efficacy end points (Table 32 and Table 33). Notably, these analyses were not controlled for multiplicity and are at risk of type I error; they should be viewed as supportive evidence in the overall assessment of patiromer.

Table 18: Outcomes on Serum Potassium — Part B (ITT Population)

Outcomes	Placebo (N = 52)	Patiromer (N = 55)
Change in serum potassium from part B baseline to part B week 4 or the first target serum potassium range of < 3.8 mmol/L or ≥ 5.5 mmol/L		
Serum potassium at part B baseline, mean (mmol/L)[a]	4.45 (0.34)	4.49 (0.43)
Estimated change in serum potassium, median (quartiles)	0.72 (0.22 to 1.22)	0.00 (−0.30 to 0.30)
Difference in median change (95% CI)	0.72 (0.46 to 0.99)	
P value	< 0.001	
Secondary efficacy outcome results		
Serum K^+ ≥ 5.5 mmol/L, stratified percentages (95% CI)	60 (47 to 74)	15 (6 to 24)
Difference (95% CI)	45 (29 to 61)	
P value[b]	< 0.001	
Serum K^+ ≥ 5.1, stratified percentages (95% CI)	91 (83 to 99)	43 (30 to 56)
Difference (95% CI)	48 (33 to 63)	
P value[b]	< 0.001	

CI = confidence interval; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.

[a]Data taken from safety set.

[b]P value was estimated with the Hochberg procedure.

Source: OPAL-HK Clinical Study Report.[8]

Exploratory Analyses of Efficacy: The exploratory outcomes relevant for this review (as per the protocol in Table 7) and those adding value are discussed subsequently.

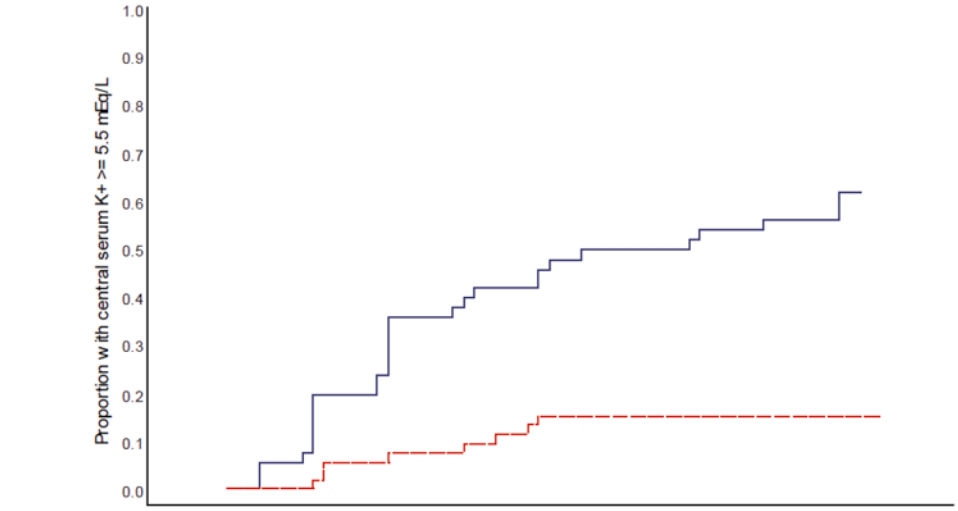
Time to First Occurrence of a Serum Potassium of 5.5 mmol/L or Greater and 5.1 mmol/L or Greater

Figure 5 and Figure 6 illustrate the time to the first occurrence of a serum potassium of 5.5 mmol/L or greater and 5.1 mmol/L or greater during part B, respectively. The Kaplan–Meier estimates showed a higher proportion of placebo-treated patients had both of these outcomes, starting at the first follow-up visit, and the difference between the treatment-group proportions increased with time.

Time to Recurrent Hyperkalemia (First Occurrence of a Serum Potassium of 5.5 mmol/L or Greater During Weeks 1 to 4 of Part B or 5.1 mmol/L or Greater During Weeks 5 to 8 of Part B)

Figure 7 shows the Kaplan–Meier plot from a time-to-event analysis performed to compare the time to recurrent hyperkalemia between the treatment groups. Recurrent hyperkalemia was defined as the first (central laboratory) serum potassium that was: 5.5 mmol/L or greater during the first 4 weeks of part B or 5.1 mmol/L or greater during the second 4 weeks of part B. The estimated proportion of patients with recurrent hyperkalemia in the placebo group was higher than in the patiromer group within the first week of part B and the difference increased with time.

Figure 5: Time to First Serum K^+ of 5.5 mmol/L or Greater — Part B (ITT Population)



Abbreviations: BBL = Part B Baseline; BW1 = Part B Week 1; BW2 = Part B Week 2; BW3 = Part B Week 3; BW4 = Part B Week 4; BW5 = Part B Week 5; BW6 = Part B Week 6; BW7 = Part B Week 7; BW8 = Part B Week 8; IP = investigational product (i.e., placebo or RLY5016 FOS); K+ = potassium; RLY5016 FOS = RLY5016 for Oral Suspension
The Kaplan-Meier (product-limit) estimates are shown. Time is defined as the target day relative to first dose of IP in Part B.

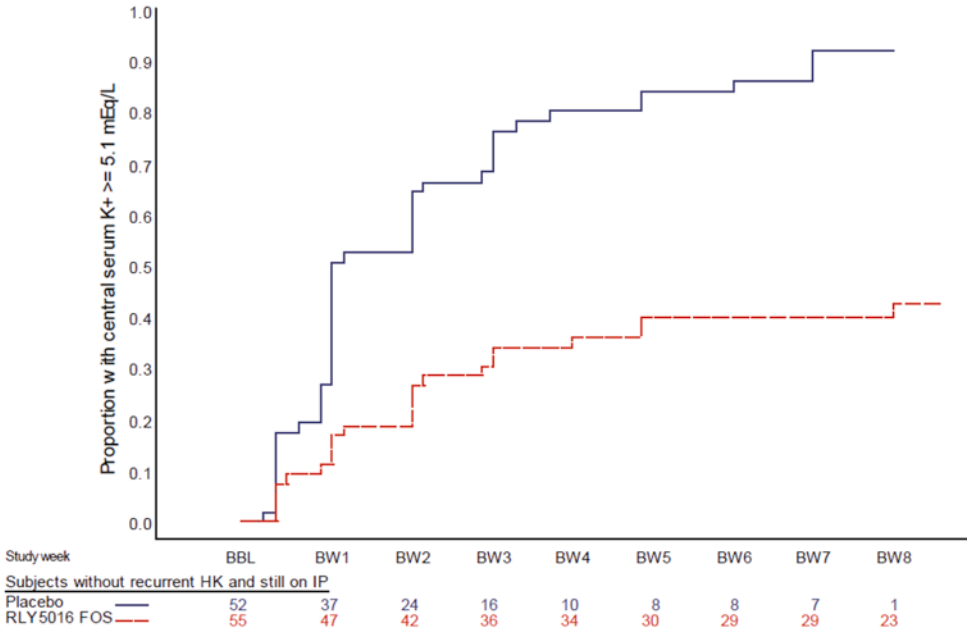
BBL = Part B baseline; BW1 = part B week 1; BW2 = part B week 2; BW3 = part B week 3; BW4 = part B week 4; BW5 = part B week 5; BW6 = part B week 6; BW7 = part B week 7; BW8 = part B week 8; HK = hyperkalemia; IP = investigational product (i.e., placebo or patiromer); K^+ = potassium; RLY5016 FOS = RLY5016 for oral suspension (patiromer).

Source: OPAL-HK Clinical Study Report.[8]

Proportion of Part B Patients Meeting Various Exploratory Outcome Definitions Regarding Serum Potassium Levels and Dose Reduction or Discontinuation of RAASi

A number of additional exploratory outcomes were assessed to determine the pattern of change in both serum potassium and RAASi dose (reduction or discontinuation) through week 8. However, these were not aimed at maintenance or restoration of the guideline-recommended maximum RAASi doses and, therefore, are not relevant, as per the protocol (Table 7). Overall, 73% of patients on patiromer did not require a modification of their RAASi or patiromer dose for recurrent hyperkalemia to complete part B, compared with 33% of patients on placebo. In the placebo group, 66% and 56% of patients had a reduction of RAASi dose or complete discontinuation of RAASi because of hyperkalemia, respectively. In contrast, 6% of patients in the patiromer group had a reduction and 6% had a discontinuation of RAASi therapy because of hyperkalemia. By the end of part B, more patiromer-treated patients (94%) were still receiving RAASi medication than patients taking placebo (44%). Similarly, a greater proportion of patients in the patiromer group received a maximum RAASi dose through the end of part B than in the placebo group: 25% versus 12%, respectively (data not presented).

Figure 6: Time to First Serum K^+ of 5.1 mmol/L or Greater — Part B (ITT Population)



Abbreviations: BBL = Part B Baseline; BW1 = Part B Week 1; BW2 = Part B Week 2; BW3 = Part B Week 3; BW4 = Part B Week 4; BW5 = Part B Week 5; BW6 = Part B Week 6; BW7 = Part B Week 7; BW8 = Part B Week 8; IP = investigational product (i.e., placebo or RLY5016 FOS); K+ = potassium; RLY5016 FOS = RLY5016 for Oral Suspension
The Kaplan-Meier (product-limit) estimates are shown. Time is defined as the target day relative to first dose of IP in Part B.

BBL = part B baseline; BW1 = part B week 1; BW2 = part B week 2; BW3 = part B week 3; BW4 = part B week 4; BW5 = part B week 5; BW6 = part B week 6; BW7 = part B week 7; BW8 = part B week 8; IP = investigational product (i.e., placebo or patiromer); K^+ = potassium; RLY5016 FOS = RLY5016 for oral suspension (patiromer).

Source: OPAL-HK Clinical Study Report.[8]

Harms

Only those harms identified in the review protocol are reported subsequently. Notably, part A and B harms data included the post-treatment follow-up period, unless mentioned otherwise. See Table 19 and Table 20 for detailed harms data.

Adverse Events

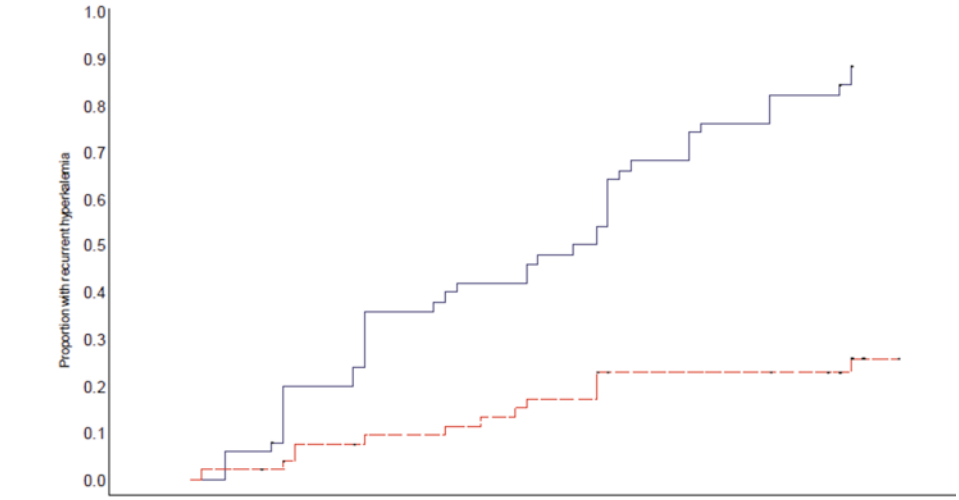
Overall, 47% patients reported a total of 224 AEs during part A, with a similar frequency in both dose groups (46% and 48% in dose group 1 and 2, respectively). The most commonly reported AEs included GI disorders and metabolism and nutrition disorders, with constipation reported for more than 5% of patients in both groups.

During part B, 50% and 47% patients in the placebo group and patiromer group experienced AEs, respectively. The frequency of any single AE was less than 5%.

Serious Adverse Events

During part A, 3 patients experienced non-fatal SAEs, 1% in each dose group; none were considered treatment related. During part B, 1 SAE was reported by a patient on placebo.

Figure 7: Time to First Recurrent Hyperkalemia — Part B (ITT Population)



BBL = part B baseline; BW1 = part B week 1; BW 2 = part B week 2; BW3 = part B week 3; BW4 = part B week 4; BW5 = part B week 5; BW6 = part B week 6; BW7 = part B week 7; BW8 = part B week 8; IP = investigational product (i.e., placebo or patiromer); HK = hyperkalemia; ITT = intention to treat; RLY 5016 FOS = RLY 5016 for oral suspension (patiromer).

Note: Recurrent HK defined as a central lab potassium of ≥ 5.5 mmol/L on days 1 to 32, or ≥ 5.1 mmol/L on day 33 to the last dose date.

Source: OPAL-HK Clinical Study Report.[8]

Withdrawals Due to Adverse Events

Overall, 6% patients in part A discontinued patiromer and 9% required a dose modification due to AEs. During part B, 1 patient in each group discontinued treatment due to AEs.

Mortality

One death was reported during part B, a 74-year-old male patient who died due to mesenteric vessel thrombosis, considered unrelated to treatment.

Notable Harms

Few of the notable harms identified in the review protocol were reported in either part of the study. Constipation was reported for 11% and 4% patients in parts A and B, respectively. Among the other notable harms, diarrhea, hypomagnesemia, and hypokalemia was reported by less than 5% of patients in either part, regardless of treatment.

Table 19: Adverse Events — Part A (Safety Set)

	OPAL-HK		
	Dose group 1	Dose group 2	Total
	5.1 mmol/L to < 5.5 mmol/L	5.5 mmol/L to < 6.5 mmol/L	5.1 mmol/L to < 6.5 mmol/L
Adverse events	N = 92	N = 151	N = 243
Patients with ≥ 1 AEs, n (%)	42 (46)	72 (48)	114 (47)
Total number of AEs	70	154	224
Most common AEs[a]			
Constipation	9 (10)	17 (11)	26 (11)
SAEs			
Patients with ≥ 1 SAEs, n (%)	1 (1)	2 (1)	3 (1)
Total number of SAEs	1	5	6
WDAEs			
WDAEs, n (%)	5 (5)	10 (7)	15 (6)
Dose modification n (%)	6 (7)	16 (11)	22 (9)
Deaths			
Number of deaths, n (%)	0	0	0
Notable harms, n (%)			
Any GI AE	15 (16)	31 (21)	46 (19)
Constipation	9 (10)	17 (11)	26 (11)
Diarrhea	2 (2)	6 (4)	8 (3)
Hypomagnesemia	3 (3)	5 (3)	8 (3)
Hypokalemia	0	3 (2)	3 (1)

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]Frequency > 5% in either group.

Source: OPAL-HK Clinical Study Report.[8]

Critical Appraisal

Internal Validity

Study Design and Conduct

The OPAL-HK study was designed in 2 sequential parts: 1 single-arm phase, where patients received 2 different doses of patiromer, followed by a randomized phase, during which patients with a higher baseline serum potassium who responded to the early patiromer treatment received placebo or continued their regular patiromer dose. The sponsor provided several arguments in favour of the study design. First, having such a 2-part design served as 1 of 2 pivotal studies required for market authorization. This design allowed the following to be evaluated: the effectiveness of patiromer for hyperkalemia treatment (part A), and the ability of patiromer to prevent the recurrence of hyperkalemia by comparing patients who continued and those who did not continue further patiromer treatment. It also allowed its safety profile to be evaluated (part B). Second, starting 1 group of patients with placebo would be considered unethical and unsafe, since all patients entering part A of the study were hyperkalemic. This rationale was justified by the fact that a higher proportion of placebo-treated patients developed recurrent hyperkalemia in part B. The withdrawal design provided a

Table 20: Adverse Events — Part B (Safety Set)

Adverse events	OPAL-HK	
	Placebo N = 52	Patiromer N = 55
Patients with ≥ 1 AEs, n (%)	26 (50)	26 (47)
Total number of AEs	49	40
Most common AEs[a]	—	—
SAEs		
Patients with ≥ 1 SAEs, n (%)	1 (2)	0
Total number of SAEs	1	0
WDAEs		
WDAEs, n (%)	1 (2)	1 (2)
Dose modification, n (%)	1 (2)	1 (2)
Deaths		
Number of deaths, n (%)	1 (2)	0
Notable harms, n (%)		
Any GI-related AE		
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Hypomagnesemia	2 (4)	1 (2)
Hypokalemia	—	—

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]No AEs reported at > 5% frequency in either group.

Source: OPAL-HK Clinical Study Report.[8]

safe and ethical way to introduce the use of a placebo in a randomized trial. The rationale and use of the randomized withdrawal design in clinical studies was based on ICH E10 Choice of Control Group and Related Issues in Clinical Trials, issued in July 2000, and found to be reasonable.[19] However, choosing an active comparator instead of placebo could have been an alternative solution (discussed more in external validity).

An IWRS was used to centrally manage the assignment of patients to treatment groups in part A, as well as to randomize patients in part B. The randomization schedule and IWRS were provided by independent third parties. Randomization was stratified to ensure an equally likely assignment of patients in the placebo and patiromer groups to each of the pre-selected randomization strata. Notably, heart failure was a key subgroup identified and reported on; however, it was not included as a strata variable in the randomization for part B, even though it was included for part A, and differences in characteristics between the patients within the heart failure subgroup in part B are likely, which could have affected the study results. The study was single-blinded; patients were blinded to their treatment assignment throughout the study, whereas study site investigators were unblinded to adequately titrate treatment doses to maintain patients' serum potassium level within the target range. To avoid potential bias resulting from the single-blinded nature of the trial, a number of pre-specified blinding procedures were implemented. Study personnel the statisticians involved in data analysis remained blinded throughout the study or until the database was locked. Additionally, no aggregated data analysis was performed until after database freeze (for part A) and database lock (for part B). The blinding plan complied with the FDA's recommendations and found to minimize introducing bias from unblinding. The placebo was packaged and administered in a manner identical to that used for patiromer. However, there was a slight difference in the colour of the 2: the placebo was white, whereas patiromer was off-white to light brown in colour. Additionally, patiromer was given at a dose of up to 50.4 g/day, while the placebo dose was fixed at 8 g/day. To minimize potential unblinding from the differences in texture and weight between the 2 treatments, patients were blinded throughout the study. It is unclear whether this would adequately prevent patients from self-identifying their treatment assignment, as those who received patiromer in part A and placebo in part B could identify the differences in the 2 treatments. Additionally, the placebo dose was not titrated to manage serum potassium, in contrast with patiromer, which was up- and down-titrated. Finally, GI side effects were more common with patiromer treatment; patients on placebo could therefore surmise their treatment assignment if they had received patiromer before. These factors may have increased the risk of unblinding. Moreover, investigators were unblinded and could consciously or unconsciously have changed their management of patients as a result. Some protocol violations were noted during the study, particularly around dose titrations and changes to RAASi therapy, which could affect the results and potentially bias the study, although sensitivity analyses were completed. While objective laboratory values were used for the outcome measures, unblinding due to differences in dose, colour, or titration protocols could have changed patient behaviours (changes in diet, interaction with health professionals), which could have affected how the patients' serum potassium values changed over time.

Baseline Characteristics and Disposition

Baseline characteristics were generally well balanced between treatment groups in both parts of the study. Even in part A, where the same treatment was assigned in a non-randomized manner, albeit at different doses, the baseline characteristics were largely similar between the dose groups. In terms of patient disposition, the 2 dose groups in part A were not compared against each other; therefore, any differences in disposition between the groups

is of less concern. A higher proportion of patients in dose group 2 entered part B of the trial compared with dose group 1, since patients in the former had a higher baseline level of serum potassium (≥ 5 mmol/L), a key criterion for entry into part B. The completion rate for each part of the study was moderate, given that 10% of patients did not complete part A and 30% did not complete part B. The completion rate was particularly low for the placebo group in part B, which is to be expected. However, when considering that the patients in part B were enriched by design to be responsive to treatment and relatively free of side effects from part A, the completion rate is rather low. Missing data and protocol violations were noted in both parts of the study, particularly for part A, where 10% of patients were lost to follow-up (i.e., did not have a central or local laboratory value at week 4) and 7% had protocol violations. Part B had few issues around missing data, with a relatively low number of patients having missing data (4 patients total), or protocol violations (< 1%). Sensitivity analyses to account for these issues (data imputation for missing serum potassium values and per-protocol analysis excluding those with a protocol violation) did not substantially change the results of the primary end point in either study phase and would therefore be expected to introduce minimal bias in the results of the primary end point.

Interventions

The use of other drugs for the treatment of hyperkalemia was excluded from this study (e.g., calcium carbonate, sevelamer, bicarbonate, and so forth). Aside from RAASi, other potassium-altering drugs (e.g., diuretics, non-selective beta blockers, amiloride, triamterene, drospirenone, nonsteroidal anti-inflammatory drugs, and digoxin) were allowed only if the dose was stabilized before screening and did not change throughout the study. Furthermore, patiromer is a non-absorbed polymer that acts locally in the GI tract and is not expected to interact with RAASis or other drugs. Any unreported use of other drugs would, therefore, have minimal effect on the efficacy results. Overall, the likelihood of confounded results from concomitant drug use is sufficiently reduced.

The Health Canada reviewer's report[2] noted that in the OPAL-HK and AMETHYST-DN trial, 32 patients with a local laboratory measurement of less than 5.5 mmol/L who were initiated with 8.4 g/day patiromer were later recognized to have a baseline serum potassium of 5.5 mmol/L or greater based on central laboratory measurement. An analysis was conducted to determine if the reduction in serum potassium differed in magnitude between those who were incorrectly assigned to an 8.4 g/day dose (n = 32) and those who were correctly assigned to a 16.8 g/day dose (n = 140); no statistically significant or clinically meaningful differences were found. A similar result was noted for 28 patients in these 2 trials who had a baseline serum potassium of 5.5 mmol/L or greater but received a starting dose of 8.4 g/day patiromer. Additionally, the sponsor was asked by the FDA to conduct a mixed-model repeated measures analysis of the integrated efficacy data from OPAL-HK and AMETHYST-DN. Results showed that the potassium-reducing effect of patiromer depended more on the baseline serum potassium level than on the dose administered (data not reported for either analysis). Together, these analyses indicate that dose mixing had a limited effect on study results and, therefore, this issue will not be explored in further detail.

Outcomes

The assessment of serum potassium appeared to be done in a standardized manner, both locally and centrally. A detailed methodology of serum potassium assessment is not provided in this review; however, Health Canada assessed the methodology in detail and indicated the methods used to analyze serum potassium levels were acceptable. The cut-off value for

change in serum potassium level from baseline (≥ 0.7 mmol/L) in part A was reasonable and in line with the FDA's established criteria.

Statistical Analysis

Overall, the statistical models used for both the primary and secondary efficacy analyses were appropriate and adjusted for several important covariates. The methods used for imputing missing data were also found to be appropriate, as noted previously, by the sensitivity analyses accounting for missing data for patients lost to follow-up. A number of additional sensitivity analyses were conducted by repeating the primary analyses in both parts, which accounted for the factors that could affect the study results. Results were always consistent with the primary analyses, demonstrating the robustness of the primary efficacy results. For part B, the analyses of the secondary efficacy end points were adjusted for multiplicity using a Hochberg correction; however, the secondary end points of part A were not controlled for type I error and should be considered as supportive evidence for the overall effect of patiromer. Moreover, no subgroup analyses were adjusted for multiplicity. As noted earlier, heart failure, which was reported as a subgroup in part B, was not included in the randomization scheme; as a result, imbalances between the groups could have been present, which could affect the results within these subgroups.

Based on the power calculation and sample size, the study had adequate power to analyze the primary efficacy outcomes for both parts.

Addressing regression to the mean: Since part A of the study was not randomized, a method was described in the sponsor's statistical analysis plan for addressing regression to the mean. However, the screening serum potassium value used to assess the inclusion of a patient into part A was determined from 2 local laboratory assessments and a separate blood draw was sent to the central laboratory to determine the part A baseline serum potassium value. It should be noted that a patient was not subsequently excluded from part A even if the serum potassium value was outside the range of 5.1 mmol/L to less than 6.5 mmol/L. According to the sponsor, this separation of screening value (determined by the local laboratory) from baseline value (determined by the central laboratory) effectively eliminated any possibility of regression to the mean. Therefore, the analyses for addressing regression to the mean was not required and are therefore not discussed in this review. While this method may improve precision by reducing random error in laboratory values, it does not take into account the fluctuations in serum potassium over time, which may cause regression to the mean. This is a potential source of bias in part A of the study, as treatment effects observed in before-and-after single-group studies may be attributable to the selective sampling of patients at a peak severity in the natural history of a disease that has a tendency to return to average severity levels over time, regardless of the interventions administered.[20] The sponsor included the baseline serum potassium value in their regression models, which would help control for regression to the mean, but may not fully eliminate this bias from the results.

External Validity

Overall, the inclusion criteria of the trial were considered highly restrictive in nature; more than 1-third of patients who were screened did not meet the screening criteria. The expert indicated that those with even worse CKD (eGFR < 15 mL/min/1.73 m^2) than OPAL-HK patients could potentially be considered for treatment in the real world if patiromer could be used freely. The trial had strict exclusion criteria in place, e.g., patients with a history of, or who currently had, certain medical conditions that were considered significant or uncontrolled, or who were taking certain potassium-altering medications, were deemed not

eligible. Therefore, the trial selected patients with the best possibility to respond to treatment with minimal side effects, and the results are not expected to be generalizable to a vast number of patients in the real world. Patients in part B were a highly enriched population; thus, large efficacy results would be expected, and the number of AEs would be expected to be lower, as those with AEs may have dropped out in part A. Patients with CKD typically have other comorbidities, and the OPAL-HK study included patients with diabetes, heart failure, and hypertension. Patients in the OPAL-HK trial were predominantly White, and none of the study sites were in Canada (although the study was partly conducted in the US); these 2 factors could limit the generalizability.

There were some generalizability concerns with respect to patiromer dosing. Patients in the OPAL-HK trial could receive up to 50.4 g of patiromer daily, although the maximum Health Canada–approved dose is 25.2 g daily. While the mean daily patiromer dose in either part was approximately 21 g, it appears that some patients received higher than the maximum approved dose. Otherwise, the choice of patiromer dose, dose administration, and titration protocol were consistent with the product monograph. Patients were instructed to reconstitute and administer patiromer as per the product monograph, which is expected in real-world use. As patients received RAASis as background medication, this also reflected the real-world situation. Since no active comparator was used in the trial, nor any indirect comparison submitted, the comparative efficacy of patiromer with other potassium-binding drugs is unclear. Based on inputs from patients and clinical groups, there is mixed evidence of the palatability, efficacy, and safety profile of patiromer compared with SPS and CPS. It should be noted that the use of SPS and CPS for the treatment of chronic hyperkalemia is limited, according to the clinical expert consulted for this review, and there is no established standard of care for mild to moderate hyperkalemia. Nonetheless, the following limitations associated with placebo trials still remain: the exaggerated effect when compared with placebo, making the clinical significance of the results more difficult to determine, and the lack of data on how patiromer compares with other treatments, which is important from a health technology assessment perspective to try to quantify the added clinical value (if any).

The trial was relatively short in duration, with approximately 12 weeks of data available. While patients could receive a maximum of 12 weeks of patiromer, the duration of placebo treatment was only 8 weeks. The short duration of the trial raises uncertainty with respect to the long-term safety and effectiveness of patiromer. However, it is recognized that continuing placebo treatment for a long period of time in hyperkalemic patients may be considered unethical. The AMETHYST-DN trial (discussed subsequently) and several other phase I and II trials used by Health Canada as part of its evidence base should be used when considering longer-term results.

Patients initially included in the trial had a mild to moderate level of hyperkalemia (5.1 mmol/L to < 6.5 mmol/L). Those who responded to part A treatment and subsequently entered part B had serum potassium of less than 5.0 mmol/L, as required by design. Since patients in the real world would not be enriched, the magnitude of the efficacy and safety profile may vary from the results of this trial. Therefore, the extent to which patients with moderate or severe hyperkalemia (serum potassium > 6.0 mmol/L) would respond to continued patiromer treatment is unclear. The clinical expert indicated that mild hyperkalemia may be treated with other means first, including dietary management. Severe hyperkalemia may require hospitalization or IV treatment. Therefore, the response in patients with moderate hyperkalemia would be most important.

Finally, the trial outcomes were based mostly on serum potassium; however, hard clinical outcomes more relevant to patients and clinicians, such as those identified in the protocol (e.g., hyperkalemia-related hospitalization and ED visits, quality of life, major adverse cardiovascular events or major adverse kidney events, and worsening of kidney disease, such as end-stage renal disease) were not assessed. While the effectiveness of patiromer on lowering serum potassium can be assessed from the trial, its effect on clinical end points is unknown, a key limitation of the findings.

Table 21 summarizes the generalizability of the evidence.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

AMETHYST-DN, a phase II study, has been summarized to provide supportive evidence regarding the efficacy and safety of patiromer to treat hyperkalemia.

Methods

AMETHYST-DN was a multi-centre, randomized, open-label, dose-ranging, phase II study for the use of patiromer to treat patients with hyperkalemia. The first patient was enrolled

Table 21: Assessment of Generalizability of Evidence for Patiromer

Domain	Factor	Evidence	CADTH's assessment of generalizability
Population	Severity of hyperkalemia, and selective population	Included patients had a mild to moderate level of hyperkalemia (5.1 mmol/L to < 6.5 mmol/L in part A, and < 5.0 mmol/L in part B). Patients in part A had to meet strict eligibility criteria; part B included responders to patiromer treatment.	The extent of the response for patients with a moderate or severe level of hyperkalemia to continued patiromer treatment is unclear. Given the restrictive trial eligibility criteria, the clinical benefits and safety profile of patiromer is unclear among unselected patients in the real world.
Intervention	Patiromer dosing	Some patients had their dose adjusted up to 50.4 g/day, which is not consistent with Health Canada product monograph.	Not a major concern, as the mean daily dose was under the maximum permitted dose of < 25 g/day.
Comparator	No active comparator	The trial compared patiromer with placebo, and no indirect comparison submitted.	The lack of an active comparator limits informing how this drug is compared with treatments used in practice, although there is limited use of an established comparator for hyperkalemia.
Outcomes	Outcome choice	All outcomes were based on serum potassium level.	Serum potassium concentrations is a surrogate outcome. It is unclear how well serum potassium change over time translates to clinical end points (reduce the risk of cardiovascular and/or kidney events).
Setting	Duration of trial	Trial duration was 12 weeks in total.	Long-term efficacy and safety uncertain.

on June 3, 2011, and the last follow-up visit was completed on June 17, 2013. In total, 304 patients from 5 countries (Croatia, Georgia, Hungary, Serbia, and Slovenia) received at least 1 dose of patiromer during the study. The TIP took place over 8 weeks and was followed by an LTMP consisting of an additional 44 weeks.

Populations

Initially, the study enrolled only patients without hyperkalemia (serum potassium ≤ 5.0 mmol/L), though it was later amended to include those with hyperkalemia who also met all other eligibility criteria.

Patients without hyperkalemia who enrolled under the original protocol were randomly assigned 3:1 to cohort 1 versus cohort 2 and began the 4-week run-in period. Patients in cohort 1 discontinued using ACEi and/or ARB medications and began losartan 100 mg/day, while patients in cohort 2 continued using ACEi and/or ARB medications in addition to starting spironolactone 25 mg/day. Patients entered the TIP and were randomized to a starting dose of patiromer when their serum potassium level was between 5.0 mmol/L and 6.0 mmol/L.

Under the protocol amendment, patients without hyperkalemia (serum potassium between 4.5 mmol/L and 5.0 mmol/L) entered cohort 1 and no additional patients were enrolled in cohort 2. Instead, additional patients with hyperkalemia (serum potassium between 5.0 mmol/L and 6.0 mmol/L) entered cohort 3, continued to use ACEi and/or ARB or other antihypertensive medications, and were randomized for treatment with patiromer without a run-in period.

Patients were eligible for AMETHYST-DN if they met the following inclusion criteria:

- male or female between 30 and 80 years old at screening
- diagnosed with T2DM after age 30 and being treated with oral medication or insulin for at least 1 year before screening
- had CKD at screening
- patients in cohorts 1 and 2 had to have a urine albumin-to-creatinine ratio of at least 30 mg/g at screening and at the beginning of the run-in period; not applicable to cohort 3
- patients in cohorts 1 and 2 had to have a serum potassium level of between 4.3 mmol/L and 5.0 mmol/L at screening, between 4.5 mmol/L and 5.0 mmol/L at the start of the run-in period, and between 5.0 mmol/L and 6.0 mmol/L at randomization; patients in cohort 3 had to have a serum potassium level of between 5.0 mmol/L and 6.0 mmol/L at either screening or the start of the run-in period
- had been taking ACEis and/or ARBs for at least 28 days before screening
- patients in cohorts 1 and 2 had to have been diagnosed with hypertension, while patients in cohort 3 could be enrolled without a diagnosis; patients with a history of hypertension had to have a systolic blood pressure between 130 mm Hg and 180 mm Hg and an average diastolic blood pressure of between 80 mm Hg and 110 mm Hg at screening and run-in
- females could not be nursing or pregnant and had to be using highly effective contraceptive for at least 3 months before, during, and 1 month after the study.

Patients were not eligible if they met any of the following exclusion criteria:

- BMI of 40 kg/m^2 or greater

- diagnosed with or laboratory measures of any of the following: type 1 diabetes, glycated hemoglobin (A1C) greater than 12% at screening (excluding patients in cohort 3 who were hyperkalemic at screening), systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg, serum magnesium less than 1.4 mg/dL at screening, urine albumin-to-creatinine ratio of 10,000 mg/g or greater at screening (excluding patients in cohort 3), renal artery stenosis, diabetic gastroparesis, non-diabetic CKD, NYHA class III or IV heart failure, liver enzymes greater than 3 times the upper limit of normal (excluding patients in cohort 3)
- history of bowel obstruction, swallowing or severe GI disorders, or major GI surgery
- emergency treatment for type 2 diabetes within the previous 3 months
- cardiac events in the previous 2 months, kidney transplant or anticipated need for transplant, cancer or history of cancer
- history of alcohol or drug abuse in the past year
- use of any of the following: loop or thiazide diuretics or other antihypertensive medications that have not been stable for at least the past 28 days before screening; polymer-based drugs, phosphate binders, other potassium binders, or anticipated use during study; lithium; potassium-sparing medication in the 7 days before screening; any investigational product within 30 days or 5 half-lives before screening.

Patient characteristics are described in Table 22. The safety population was made up of 304 patients who had an overall mean (SD) age of 66.3 (8.61) years. In general, more males (63.2%) than females (36.8%) were enrolled and 100% of patients were White. Most patients had stage 3 or 4 CKD and the mean (SD) time since CKD diagnosis was approximately 3 (3.5) years. All patients had T2DM with a mean (SD) time since diagnosis of more than 13 (8.03) years. Most patients (65.5%) were not diagnosed with heart failure, and those who were diagnosed had NYHA class I (8.6%) or class II (26.0%).

Interventions

The study medication was provided as individual packets, each containing 4.2 g of patiromer as a powder that was to be mixed with an appropriate, low-potassium drink or food before being administered orally. Based on baseline serum potassium, patients were randomly assigned to 1 of 2 strata, each containing 3 different doses of patiromer. Starting doses of patiromer for stratum 1 (serum potassium > 5.0 mmol/L to 5.5 mmol/L) included 8.4 g per day, 16.8 g per day, and 25.2 g per day. For those in stratum 2 (serum potassium > 5.5 mmol/L to < 6.0 mmol/L), patients could receive a starting dose of 16.8 g/day, 25.2 g/day, or 33.6 g/day. Note that patiromer 33.6 g/day is outside the Health Canada–approved dose range. Doses could be adjusted during the treatment period to maintain serum potassium levels within the target range.

Patients in cohort 1 discontinued ACEi and/or ARB treatment while starting losartan 100 mg/day during the TIP. Patients in cohort 2 continued their current, but started no new, ACEi and/or ARB medication while starting spironolactone 25 mg/day. For those in either cohort 1 or 2 who did not have blood pressure measuring in the target range of 130/80 mm Hg, spironolactone 25 mg/day was started or increased to 50 mg/day. If patients experienced symptomatic hypotension (systolic blood pressure < 110 mm Hg), they were able to reduce their spironolactone dose by half. Patients in cohort 3 continued their current, but started no new, ACEi and/or ARB treatment during the study and were not required to take either losartan or spironolactone.

Table 22: Summary of Baseline Characteristics in AMETHYST-DN (Safety Population)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L				Total
	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)	(N = 304)
Age, mean (SD)	66.7 (7.55)	65.9 (9.67)	66.9 (9.01)	66.5 (8.75)	66.2 (5.58)	66.3 (9.61)	65.0 (8.98)	65.8 (8.24)	66.3 (8.61)
Sex, n (%)									
Male	45 (60.8)	47 (64.4)	47 (64.4)	139 (63.2)	18 (69.2)	15 (53.6)	20 (66.7)	53 (63.1)	192 (63.2)
Female	29 (39.2)	26 (35.6)	26 (35.6)	81 (36.8)	8 (30.8)	13 (46.4)	10 (33.3)	31 (36.9)	112 (36.8)
Race, n (%)									
White	74 (100.0)	73 (100.0)	73 (100.0)	220 (100.0)	26 (100.0)	28 (100.0)	30 (100.0)	84 (100.0)	304 (100.0)
Disease history									
CKD stage, n (%)									
1	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
2	7 (9.5)	8 (11.0)	7 (9.6)	22 (10.0)	2 (7.7)	2 (7.1)	3 (10.0)	7 (8.3)	29 (9.5)
3a	24 (32.4)	18 (24.7)	26 (35.6)	68 (30.9)	6 (23.1)	6 (21.4)	5 (16.7)	17 (20.2)	85 (28.0)
3b	24 (32.4)	35 (47.9)	25 (34.2)	84 (38.2)	8 (30.8)	11 (39.3)	8 (26.7)	27 (32.1)	111 (36.5)
4	14 (18.9)	12 (16.4)	13 (17.8)	39 (17.7)	8 (30.8)	7 (25.0)	12 (40.0)	27 (32.1)	66 (21.7)
5	2 (2.7)	0 (0.0)	0 (0.0)	2 (0.9)	2 (7.7)	1 (3.6)	1 (3.3)	4 (4.8)	6 (2.0)
Time since CKD diagnosis (years), mean (SD)	2.7 (2.75)	3.2 (5.12)	2.4 (2.61)	2.8 (3.67)	3.5 (3.25)	2.7 (2.46)	3.4 (3.21)	3.2 (2.98)	2.9 (3.50)
Time since T2DM diagnosis (years), mean (SD)	13.0 (7.69)	12.2 (8.30)	12.5 (7.08)	12.6 (7.68)	14.6 (8.03)	13.6 (8.54)	15.3 (9.78)	14.5 (8.78)	13.1 (8.03)
Heart failure, n (%)									
NYHA class I	5 (6.8)	6 (8.2)	7 (9.6)	18 (8.2)	3 (11.5)	4 (14.3)	1 (3.3)	8 (9.5)	26 (8.6)
NYHA class II	21 (28.4)	17 (23.3)	21 (28.8)	59 (26.8)	5 (19.2)	7 (25.0)	8 (26.7)	20 (23.8)	79 (26.0)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L				Total
	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)	(N = 304)
No	48 (64.9)	50 (68.5)	45 (61.6)	143 (65.0)	18 (69.2)	17 (60.7)	21 (70.0)	56 (66.7)	199 (65.5)

CKD = chronic kidney disease; NYHA = New York Heart Association; SD = standard deviation; T2DM = type 2 diabetes mellitus.

[a]Not within the Health Canada–approved dose range.

Source: AMETHYST-DN Clinical Study Report.[21]

Other concomitant medications permitted included antidiabetic treatments, nonsteroidal anti-inflammatory drugs, laxatives, contraceptives, and drugs for pre-existing conditions that were not part of the exclusion criteria.

Outcomes

The primary efficacy variable for the TIP was the change in serum potassium from baseline to the time before dose titration or week 4, while the primary safety variable for the LTMP was the frequency and severity of AEs.

The secondary efficacy variable for the TIP was the mean change in serum potassium level from baseline to dose titration or week 8. The secondary efficacy variables for the LTMP included the mean change in serum potassium level from baseline to post-baseline visits and the mean change in serum potassium level from the end of the treatment follow-up visits.

Statistical Analysis

Quantitative variables were summarized by mean and SD. Qualitative variables were described as number and percentage of patients in each category. Statistical significance testing was 2-sided, using an alpha of 0.05 within each starting dose, and P values were reported. For the mean change in serum potassium from baseline to weeks 4 and 8, parallel lines analysis of covariance models were used within each stratum. Covariates included the treatment factor and baseline serum potassium value. The least squares mean estimates from baseline to weeks 4 and 8 and 95% CIs were calculated. A paired t-test was used to determine if the mean serum potassium change from baseline was not equal to zero and a Fisher's exact test for comparisons of proportions was used within each stratum. There was no adjustment for multiplicity in this study and patients who had missing laboratory values were removed from analysis.

The safety population (N = 304) was made up of all patients who were randomized and received at least 1 dose of patiromer. The modified ITT population (N = 304) included all patients who were randomized to a starting dose group and received at least 1 dose of patiromer. The per-protocol population (N = 241) consisted of all patients who demonstrated between 80% and 120% adherence with taking patiromer. Patients who discontinued patiromer early had their last observed data as the end points.

Patient Disposition

In total, 535 patients were screened for AMETHYST-DN, 324 patients were enrolled in any of the 3 cohorts, and 306 patients were randomized to receive patiromer. Table 23 outlines the number of patients randomized to each of the starting doses of patiromer by the 3 cohorts. Three patients who entered cohort 2, which was subsequently deactivated, were included in cohort 1.

Patient disposition is outlined in Table 24. Overall, 86.9% of all randomized patients completed the TIP, 64.4% completed the LTMP, 69.0% completed the entire study, and completion rates were slightly higher for stratum 1 compared with stratum 2. Withdrawal of consent was the most common reason for discontinuation from the study (10.1%). Other reasons included AE (6.2%), non-compliance (3.6%), death (2.6%), high serum potassium (2.3%), low serum potassium (2.3%), abnormal renal function (1.3%), and other reasons (2.0%). Discontinuation rates were mostly similar across the doses within each stratum, though the overall rates were generally higher in stratum 2 except for withdrawal of consent, non-compliance, and other reasons.

Exposure to Study Treatments

Over the course of the entire study treatment period, patients were exposed to patiromer for a mean (SD) of 270.2 (140.86) days and 265.3 (138.35) days in strata 1 and 2, respectively (Table 25). The majority of patients demonstrated 80% or greater adherence to the study drug: 94.5% in stratum 1 and 90.5% in stratum 2.

Efficacy

Efficacy was assessed by measurement of serum potassium levels at different time points (Table 26). The mean (SD) serum potassium measurements at baseline were 5.15 mmol/L (0.251 mmol/L) and 5.66 mmol/L (0.359 mmol/L) for strata 1 and 2, respectively. At week 4, the mean (SD) change from baseline levels was −0.47 mmol/L (0.601 mmol/L) and −0.92 mmol/L (0.748 mmol/L) for the 2 strata, and at week 8 was −0.45 mmol/L (0.626 mmol/L) and −0.91 mmol/L (0.771 mmol/L).

Table 27 summarizes the mean serum potassium at the end of treatment and mean change 28 days later. At the end of treatment, the mean (SD) serum potassium levels for strata 1 and 2 were similar at 4.61 mmol/L (0.429 mmol/L) and 4.57 mmol/L (0.549 mmol/L), respectively, and were similar among the different doses in each stratum. At 28 days post-treatment, mean levels increased for all dose groups of patiromer.

Figure 8 and Figure 9 show the mean serum potassium during the entire treatment period and follow-up for patients in strata 1 and 2, respectively. Follow-up visits included patients who discontinued patiromer at any point during the study.

Harms

Safety and tolerability were monitored by frequency and severity of AEs and have been summarized in Table 28. Overall, 65.8% of patients in stratum 1 and 77.4% of patients in stratum 2 experienced an AE. GI-related AEs occurred most frequently. Two patients in each of the TIP and LTMP experienced GI perforation, ulceration, hemorrhage, or obstruction. A total of 15 deaths occurred, 9 (4.1%) in stratum 1 and 6 (7.1%) in stratum 2. Serious AEs (SAEs) were reported in 13.2% and 17.9% of patients in strata 1 and 2, respectively.

Table 23: Number of Patients by Stratum, Cohort, and Starting Dose in AMETHYST-DN (All Randomized Patients)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L				Total
	8.4 (N = 74)	16.8 (N = 74)	25.2 (N = 74)	Overall (N = 222)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)	(N = 306)
Cohort 1	16	15	16	47	2	4	5	11	58
Cohort 2	1	1	1	3	0	0	0	0	3
Cohort 3	57	58[b]	57[b]	172	24	24	25	73	245

[a]Not within the Health Canada–approved dose range.

[b]Two patients were randomized, but never received a dose of patiromer. These patients were excluded from the mITT population.

Source: AMETHYST-DN Clinical Study Report.[21]

Table 24: Summary of Patient Disposition in AMETHYST-DN (All Randomized Patients)

	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L				
Patiromer starting dose (g/day)	8.4 (N = 74)	16.8 (N = 74)	25.2 (N = 74)	Overall (N = 222)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)	Total (N = 306)
Screened	–	–	–	–	–	–	–	–	535
Enrolled	–	–	–	–	–	–	–	–	324
Randomized	–	–	–	–	–	–	–	–	306
Safety population, n (%)	74 (100.0)	73 (98.6)	73 (98.6)	220 (99.1)	26 (100.0)	28 (100.0)	30 (100.0)	84 (100.0)	304 (99.3)
mITT population, n (%)	74 (100.0)	73 (98.6)	73 (98.6)	220 (99.1)	26 (100.0)	28 (100.0)	30 (100.0)	84 (100.0)	304 (99.3)
PP population, n (%)	58 (78.4)	62 (83.8)	62 (83.8)	182 (82.0)	20 (76.9)	22 (78.6)	17 (56.7)	59 (70.2)	241 (78.8)
Completed TIP, n (%)	64 (86.5)	65 (87.8)	65 (87.8)	194 (87.4)	24 (92.3)	25 (89.3)	23 (76.7)	72 (85.7)	266 (86.9)
Completed LTMP, n (%)	51 (68.9)	50 (67.6)	46 (62.2)	147 (66.2)	15 (57.7)	20 (71.4)	15 (50.0)	50 (59.5)	197 (64.4)
Completed study,[b] n (%)	56 (75.7)	51 (68.9)	50 (67.6)	157 (70.7)	17 (65.4)	21 (75.0)	16 (53.3)	54 (64.3)	211 (69.0)
Discontinued study,[c] n (%)									
Adverse event	4 (5.4)	2 (2.7)	7 (9.5)	13 (5.9)	2 (7.7)	2 (7.1)	2 (6.7)	6 (7.1)	19 (6.2)
Death	1 (1.4)	0 (0.0)	4 (5.4)	5 (2.3)	1 (3.8)	2 (7.1)	0 (0.0)	3 (3.6)	8 (2.6)
Abnormal renal function	0 (0.0)	2 (2.7)	0 (0.0)	2 (0.9)	1 (3.8)	0 (0.0)	1 (3.3)	2 (2.4)	4 (1.3)
High serum potassium	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)	2 (7.7)	0 (0.0)	2 (6.7)	4 (4.8)	7 (2.3)
Low serum potassium	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)	1 (3.8)	0 (0.0)	3 (10.0)	4 (4.8)	7 (2.3)
Non-compliance	3 (4.1)	4 (5.4)	3 (4.1)	10 (4.5)	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.2)	11 (3.6)
Withdrawal of consent	6 (8.1)	12 (16.2)	5 (6.8)	23 (10.4)	2 (7.7)	2 (7.1)	4 (13.3)	8 (9.5)	31 (10.1)
Other	2 (2.7)	1 (1.4)	2 (2.7)	5 (2.3)	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.2)	6 (2.0)

LTMP = long-term maintenance plan; mITT = modified intention to treat; PP = per protocol; TIP = treatment initiation period.

[a]Not within the Health Canada–approved dose range.

[b]Ten patients from stratum 1 and 4 patients from stratum 2 completed the TIP (and thus, the entire study) before the protocol amendment extending the study to 52 weeks and did not enter the LTMP.

[c]Occurring in greater than 2% of patients.
Source: AMETHYST-DN Clinical Study Report.[21]

Critical Appraisal

Internal Validity

AMETHYST-DN was a multi-centre, open-label, dose-ranging study investigating the long-term use of patiromer in patients with hyperkalemia. Patients were randomized to the different dose groups within each stratum, but there was no blinding and patients were aware they were receiving active treatment. Moreover, the protocol was changed partway through to include individuals with hyperkalemia and, as a result, there was no guarantee the patients enrolled early in the trials would be similar to patients enrolled in the later stages of the trial. Thus, heterogeneity in the patient populations is to be expected, which could have affected the study results. With no adjustment for multiplicity in this study, there was a high risk for type I errors. Patients were removed from analysis if they had missing baseline values (n = 3) or if there were no central laboratory results available before titration (n = 1). Though few, the exclusion of these 4 patients combined with the large number of dropouts could affect how the safety and long-term efficacy results are interpreted. Given that the product was available in individual packets, each containing 4.2 g of patiromer, it is possible that individuals could infer what dose they were assigned, based on how many packets they used. This knowledge may have resulted in behavioural changes in patients (e.g., diet, other medications), which may have affected the results obtained. It should also be noted that the 33.6 g/day dose of patiromer is outside the Health Canada–approved dose range. The primary efficacy end point was met with a statistically significant least squares mean decrease in serum potassium from baseline to week 4 for all dose groups and strata (P < 0.001). Adherence appeared to be good among the patients who remained in the study, with more than 90% of patients having

Table 25: Summary of Exposure to Patiromer in AMETHYST-DN (Safety Population)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L			
	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)
Entire course of study treatment								
Duration of exposure (days), mean (SD)	254.1 (154.23)	286.4 (129.89)	270.4 (137.22)	270.2 (140.86)	279.1 (125.98)	292.0 (127.55)	228.3 (153.85)	265.3 (138.35)
Daily dose (g/day), mean (SD)	14.3 (7.91)	18.9 (9.01)	25.0 (6.75)	19.4 (9.05)	20.4 (7.82)	29.5 (10.41)	31.0 (10.69)	27.2 (10.75)
Dosing adherence,[b] mean (SD)	97.4 (8.88)	96.0 (10.89)	97.8 (7.12)	97.0 (9.08)	94.5 (15.93)	96.5 (8.35)	91.9 (21.40)	94.3 (16.21)
≥ 80% adherence,[b] n (%)	70 (94.6)	68 (93.2)	70 (95.9)	208 (94.5)	24 (92.3)	26 (92.9)	26 (86.7)	76 (90.5)

SD = standard deviation.

[a]Not within the Health Canada–approved dose range.

[b]Calculated as the total number of sachets dispensed that the patient consumed divided by the number of sachets they should have taken, multiplied by 100.

Source: AMETHYST-DN Clinical Study Report.[21]

Table 26: Mean Change in Serum Potassium From Baseline in AMETHYST-DN (mITT Population)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L			
	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)
Baseline[b] serum potassium (mmol/L)								
Number of patients, n (%)	73 (98.6)	73 (100)	72 (98.6)	218 (99.0)	26 (100)	27 (96.4)	30 (100)	83 (98.8)
Mean (SD)	5.14 (0.259)	5.17 (0.247)	5.14 (0.249)	5.15 (0.251)	5.70 (0.376)	5.68 (0.312)	5.61 (0.389)	5.66 (0.359)
Week 4 or time to first titration serum potassium (mmol/L): Change from baseline[c]								
Number of patients, n (%)	73 (98.6)	72 (98.6)	72 (98.6)	217 (98.6)	26 (100)	27 (96.4)	30 (100)	83 (98.8)
Mean (SD)	−0.35 (0.590)	−0.53 (0.650)	−0.54 (0.548)	−0.47 (0.601)	−0.90 (0.637)	−0.98 (0.634)	−0.88 (0.930)	−0.92 (0.748)
LSM ± SEd	−0.35 ± 0.066	−0.51 ± 0.067	−0.55 ± 0.067	−0.47 ± 0.039	−0.87 ± 0.134	−0.97 ± 0.132	−0.92 ± 0.125	−0.92 ± 0.075
95% CId	−0.48 to −0.22	−0.64 to −0.38	−0.68 to −0.42	−0.55 to −0.40	−1.14 to −0.60	−1.23 to −0.70	−1.17 to −0.67	−1.07 to −0.77
P valued,e	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Comparison with low dose[d]								
LSMD	—	−0.16	−0.20	—	—	−0.10	−0.05	—
95% CI	—	−0.35 to 0.03	−0.39, −0.01	—	—	−0.47 to 0.28	−0.42 to 0.31	—
P value	—	0.093	0.035	—	—	0.602	0.777	—
Comparison with medium dose[d]								
LSMD	—	—	−0.04	—	—	—	0.05	—
95% CI	—	—	−0.23 to 0.15	—	—	—	−0.32 to 0.41	—
P value	—	—	0.663	—	—	—	0.801	—
Week 8 or time to first titration serum potassium (mmol/L): Change from baseline[c]								
Number of patients, n (%)	73 (98.6)	72 (98.6)	72 (98.6)	217 (98.6)	26 (100)	27 (96.4)	30 (100)	83 (98.8)
Mean (SD)	−0.34 (0.599)	−0.49 (0.668)	−0.53 (0.602)	−0.45 (0.626)	−0.91 (0.664)	−0.97 (0.653)	−0.87 (0.955)	−0.91 (0.771)
LSM ± SEd	−0.35 ± 0.070	−0.47 ± 0.070	−0.54 ± 0.070	−0.45 ± 0.040	−0.88 ± 0.142	−0.95 ± 0.139	−0.91 ± 0.132	−0.91 ± 0.079

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L			
	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)
95% CId	−0.48, −0.21	−0.61, −0.33	−0.68, −0.40	−0.53, −0.37	−1.16, −0.60	−1.23, −0.68	−1.17, −0.64	−1.07, −0.76
P valued,e	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Comparison with low dose[d]								
LSMD	—	−0.13	−0.20	—	—	−0.07	−0.03	—
95% CI	—	−0.32 to 0.07	−0.39 to −0.00	—	—	−0.47 to 0.32	−0.42 to 0.36	—
P value	—	0.201	0.048	—	—	0.709	0.885	—
Comparison with medium dose[d]								
LSMD	—	—	−0.07	—	—	—	0.05	—
95% CI	—	—	−0.27 to 0.13	—	—	—	−0.34 to 0.43	—
P value	—	—	0.484	—	—	—	0.811	—

ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intention to treat; LSM = least squares mean; LSMD = least squares mean difference; SD = standard deviation, SE = standard error.

[a]Not within the Health Canada–approved dose range.

[b]Baseline represents last available measurement before start of patiromer administration.

[c]For patients who required patiromer dose titration before this time point (week 4 or 8), the end point was the last observed data before the first titration. For patients who prematurely discontinued the study drug without dose titration and before this time point (week 4 or 8), the end point was the last observed post-baseline data before termination.

[d]Generated from a parallel lines ANCOVA model using a fixed effect for randomized starting dose and baseline serum potassium value as a covariate.

[e]P value was to test if LSM was not equal to zero.

Source: AMETHYST-DN Clinical Study Report.[21]

80% or greater adherence during the 52 weeks of treatment, though there was still a large number of dropouts (nearly 30% from either stratum).

External Validity

All of the study population was White and patients were recruited from 5 countries in Europe. Eligibility was restricted to patients who were between 30 and 80 years old, diagnosed with type 2 diabetes and CKD, and who had a BMI no greater than 40 kg/m^2. Patients could not have a serum potassium greater than 6.0 mmol/L, and patients with NYHA classes III or IV heart failure were excluded. Therefore, it may not be reasonable to extend the safety and efficacy results to individuals with hyperkalemia outside of these criteria without further investigation into these populations. There was also a large proportion of screening failures, with little information explaining the failures.

Discussion

Summary of Available Evidence

One phase III trial was included in the review, OPAL-HK, which was a 2-part, single-blind study designed to assess the efficacy and safety of patiromer in 243 patients with hyperkalemia (5.1 mmol/L to < 6.5 mmol/L serum potassium) and CKD (15 ≤ eGFR < 60 mL/min/1.73 m^2) who were receiving a stable dose of an RAASi. Part A assessed the effects of 4 weeks of patiromer treatment on lowering serum potassium levels, during which all patients received patiromer based on their baseline serum potassium level: those with 5.1 mmol/L to less than 5.5 mmol/L received a starting dose of 8.4 g/day patiromer, whereas those with 5.5 mmol/L to less than 6.5 mmol/L received 16.8 g/day patiromer. Patients (n = 107) who responded to treatment in part A (achieved serum potassium within the target range of 3.8 mmol/L to < 5.1 mmol/L) and had a serum potassium of ≥ 5.5 mmol/L at the beginning of part A entered into part B. Part B was designed to evaluate whether 8 weeks of patiromer treatment was necessary to maintain serum potassium control and evaluate the effects that withdrawing patiromer had on serum potassium control. Patients in part B were randomized to receive either patiromer at their regular doses or placebo at a fixed dose of 8 g/day. Throughout the study, the patiromer dose could be titrated, from a minimum daily dose of 0 g to a maximum of 50.4 g, to maintain serum potassium within the target range. In contrast, RAASi dose was generally not titrated in part A, but was allowed to be adjusted in part B, and placebo dose was never titrated. Most efficacy end points were based on serum potassium level: the primary efficacy outcome was the change in serum potassium from baseline to week 4 of the respective parts, and the secondary efficacy outcomes were the proportions of patients with a target level of serum potassium at the end of the respective parts. In terms

Table 27: Mean Change in Serum Potassium From End of Treatment to Follow-Up Visits in AMETHYST-DN (mITT Population, Patients Who Entered Follow-Up)

Patiromer starting dose (g/day)	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L			
	8.4 (N = 60)	16.8 (N = 55)	25.2 (N = 57)	Overall (N = 172)	16.8 (N = 23)	25.2 (N = 20)	33.6[a] (N = 23)	Overall (N = 66)
End of treatment[b] serum potassium (mmol/L)								
Number of patients, n (%)	60 (100)	55 (100)	57 (100)	172 (100)	23 (100)	20 (100)	23 (100)	66 (100)
Mean (SD)	4.55 (0.517)	4.69 (0.537)	4.60 (0.429)	4.61 (0.497)	4.55 (0.576)	4.61 (0.357)	4.54 (0.667)	4.57 (0.549)
Follow-up +28 days serum potassium (mmol/L)								
Number of patients, n (%)	45 (75.0)	41 (74.5)	40 (70.2)	126 (73.3)	15 (65.2)	17 (85.0)	15 (65.2)	47 (71.2)
Change from end of treatment, mean (SD)	0.55 (0.455)	0.37 (0.474)	0.34 (0.419)	0.43 (0.456)	0.29 (0.724)	0.38 (0.519)	0.82 (0.730)	0.49 (0.685)

mITT = modified intention to treat; SD = standard deviation.

[a]Not within the Health Canada–approved dose range.

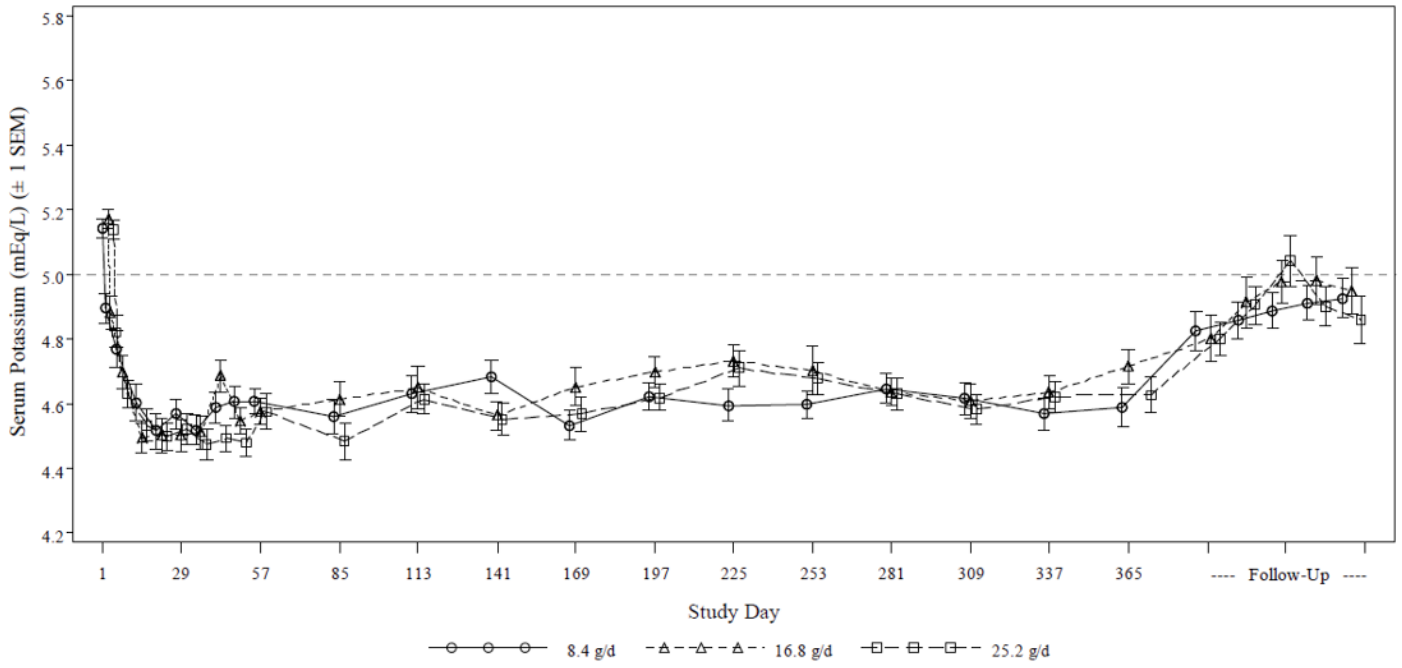
[b]The end of treatment value was the last available serum potassium value on (+1 day) or before the last dose received over the entire course of study treatment.

Source: AMETHYST-DN Clinical Study Report.[21]

of limitations, the following internal validity issues are noteworthy: the single-arm design and potential regression to the mean in part A; missing data throughout both arms that may have affected the study results, although handled with acceptable methods; and potential unblinding during part B of the study, which could have affected the study results. There were 3 major limitations with respect to generalizability. The trial restricted patients with significant comorbidities from being included; many patients with CKD may not meet the eligibility criteria. Furthermore, patients in part B were selected on the basis of their response in part A, which may have inflated the effects of patiromer while minimizing side effects, which would not be the case in the real world. The total duration of the trial was relatively short, with approximately 12 weeks of data available. The outcomes were all based on serum potassium; however, clinical outcomes more relevant to clinicians and patients were not addressed. Overall, the results should be interpreted in the context of the patients who did not drop out and were selected (in both parts) by design to show greater efficacy and fewer side effects.

One phase II trial, AMETHYST-DN, provided supportive evidence with long-term data. This was a randomized, open-label, dose-ranging study for the use of patiromer to treat patients with hyperkalemia. The study consisted of 2 patiromer treatment periods: an 8-week TIP followed by a 44-week LTMP. Patients were assigned to 1 of 2 strata according to their baseline serum potassium levels and initiated patiromer treatment at 3 randomly assigned starting doses per stratum (stratum 1: 8.4 g/day to 25.2 g/day; stratum 2: 16.8 g/day to 33.6 g/day). The primary efficacy outcome was the change in serum potassium from baseline to the time before dose titration or week 4, while the primary safety outcome for the LTMP was the frequency and severity of AEs. The inclusion criteria were largely similar to OPAK-HK: patients with T2DM or CKD who were receiving ACEi and/or ARB (2 main RAASi types) with or without

Figure 8: Mean Serum Potassium During Treatment Period and Follow-Up by Randomized Starting Dose (Stratum 1) in AMETHYST-DN (mITT Population)



mITT = modified intention to treat; SEM = standard error of the mean.
Source: AMETHYST-DN Clinical Study Report.[21]

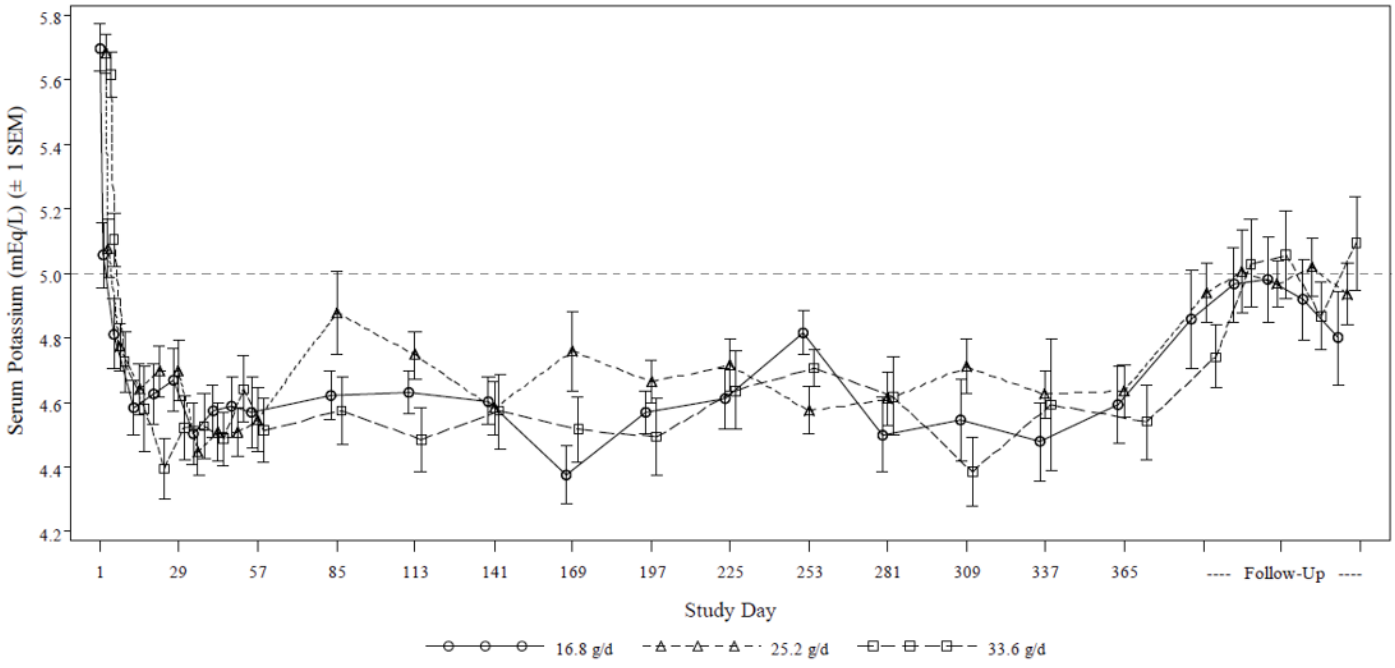
spironolactone were included. This trial had 8 weeks of efficacy data from 266 patients and 1 year of efficacy and safety data from 197 patients; this would be useful to evaluate the efficacy and safety profile of patiromer over a long period of time. Major limitations of the trial include its open-label design, potential heterogeneity among patients resulting from protocol changes partway through the study, no adjustment for multiplicity, high proportion of dropouts, and a large proportion of screening failures.

Interpretation of Results

Efficacy

OPAL-HK part A was a 4-week single-arm, single-blind phase, during which patients received 8.4 g or 16.8 g of patiromer daily if their baseline serum potassium was 5.1 mmol/L to less than 5.5 mmol/L or 5.5 mmol/L to less than 6.5 mmol/L, respectively. While both dose groups had a reduction in serum potassium from baseline after 4 weeks of patiromer treatment, a statistical test for change from baseline in serum potassium was performed by collapsing the 2 groups, consistent with the design feature. It is therefore unclear if patiromer has a similar potassium-lowering effect on those with mild hyperkalemia (5.1 mmol/L to < 5.5 mmol/L) as on those with borderline moderate hyperkalemia (≥ 5.5 mmol/L). Notably, serum potassium in dose group 1 was reduced by 0.65 mmol/L from baseline, which did not meet the pre-specified cut-off value of 0.7 mmol/L or greater set by the FDA as the level needed to consider a clinically meaningful effect. Therefore, the reduction in serum potassium from baseline in part A was primarily driven by dose group 2, where a mean reduction of 1.23 mmol/L was observed. This was reinforced by the subgroup results, which showed baseline serum

Figure 9: Mean Serum Potassium During Treatment Period and Follow-Up by Randomized Starting Dose (Stratum 2) in AMETHYST-DN (mITT Population)



mITT = modified intention to treat; SEM = standard error of the mean.
Note: 33.6 g/day is not within the Health Canada–approved dose range.
Source: AMETHYST-DN Clinical Study Report.[21]

potassium was the only factor that statistically significantly affected the level of change in serum potassium from baseline. Nonetheless, the primary efficacy outcome for part A was met, as the reduction in serum potassium from baseline was higher than the FDA's specified cut-off value (1.01 mmol/L; P < 0.001). The clinical expert consulted for this review indicated that patients with mild hyperkalemia, such as those with less than 5.5 mmol/L, are unlikely to be considered for patiromer treatment.

In part A, 76% of patients met the secondary efficacy outcome, i.e., achieved a serum potassium level within the target range (3.8 mmol/L to < 5.1 mmol/L) at the end of the 4-week treatment period. Nonetheless, the clinical expert indicated that a 76% success rate was clinically important. Notably, this analysis was not adjusted for type I error; results should

Table 28: Summary of Safety Outcomes in AMETHYST-DN (Safety Population)

	Stratum 1 Serum potassium > 5.0 mmol/L to 5.5 mmol/L				Stratum 2 Serum potassium > 5.5 mmol/L to < 6.0 mmol/L			
Patiromer starting dose (g/day)	8.4 (N = 74)	16.8 (N = 73)	25.2 (N = 73)	Overall (N = 220)	16.8 (N = 26)	25.2 (N = 28)	33.6[a] (N = 30)	Overall (N = 84)
AE, n (%)	47 (63.5)	51 (69.9)	48 (65.8)	146 (66.4)	18 (69.2)	22 (78.6)	25 (83.3)	65 (77.4)
TIP, N	74	73	73	220	26	28	30	84
≥ 1 GI event	8 (10.8)	6 (8.2)	6 (8.2)	20 (9.1)	2 (7.7)	3 (10.7)	7 (23.3)	12 (14.3)
Constipation	3 (4.1)	3 (4.1)	2 (2.7)	8 (3.6)	1 (3.8)	1 (3.6)	5 (16.7)	7 (8.3)
Diarrhea	2 (2.7)	2 (2.7)	1 (1.4)	5 (2.3)	2 (7.7)	0 (0.0)	1 (3.3)	3 (3.6)
GI perforation, ulceration, hemorrhage, obstruction	0 (0.0)	1 (1.4)	1 (1.4)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LTMP, N	58	63	59	180	22	24	20	66
≥ 1 GI event	7 (12.1)	7 (11.1)	5 (8.5)	19 (10.6)	3 (13.6)	1 (4.2)	2 (10.0)	6 (9.1)
Constipation	1 (1.7)	0 (0.0)	2 (3.4)	3 (1.7)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.5)
Diarrhea	4 (6.9)	3 (4.8)	0 (0.0)	7 (3.9)	1 (4.5)	1 (4.2)	0 (0.0)	2 (3.0)
GI perforation, ulceration, hemorrhage, obstruction	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.5)
Resulting in death	1 (1.4)	2 (2.7)	6 (8.2)	9 (4.1)	1 (3.8)	4 (14.3)	1 (3.3)	6 (7.1)
Leading to discontinuation	6 (8.1)	6 (8.2)	8 (11.0)	20 (9.1)	2 (7.7)	1 (3.6)	5 (16.7)	8 (9.5)
SAE, n (%)	9 (12.2)	10 (13.7)	10 (13.7)	29 (13.2)	6 (23.1)	5 (17.9)	4 (13.3)	15 (17.9)
GI disorders	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (3.6)	1 (3.3)	2 (2.4)

AE = adverse event; GI = gastrointestinal; LTMP = long-term maintenance period; SAE = serious adverse event; TIP = treatment initiation period.

[a]Not within the Health Canada–approved dose range.

Source: AMETHYST-DN Clinical Study Report.[21]

therefore be interpreted in view of this and should be considered only to provide additional context on the potassium-lowering effect of patiromer.

Additional analysis in part A showed there was a substantial reduction in serum potassium within a few days (3 days) after the first patiromer treatment, regardless of starting dose. The gradual decrease in serum potassium continued until the third week, after which the level of serum potassium remained relatively flat. Results from exploratory analysis showed that the majority (88%) of patients had a maximum serum potassium reduction, defined in the study as a reduction of greater than 0.5 mmol/L. While the maximum reduction in serum potassium included the FDA's cut-off for clinical significance, as per the primary efficacy analysis (≥ 0.7 mmol/L), the chosen cut-off for maximum reduction in serum potassium made it difficult to evaluate what percentage of patients achieved the clinically meaningful effect. Nonetheless, these analyses were exploratory and should only be considered to provide additional context on the potassium-lowering effect of patiromer.

Eligible patients entered part B of the trial if their serum potassium level was within the target range in part A (3.8 mmol/L to < 5.1 mmol/L) and they had a baseline serum potassium level greater than 5.5 mmol/L, among other criteria. Therefore, the patient population, although aligned with the objective of part B, is a selective population. Following 4 weeks of treatment, the placebo group had an increase in serum potassium from baseline, whereas the patients in the patiromer group maintained their serum potassium level. The difference between patiromer and placebo with respect to mean change from baseline in serum potassium (0.72 mmol/L) was statistically significant. Given the natural history of the disease, a stable form of hyperkalemia does not reverse over time; therefore, any difference observed between treatment groups was attributable to patiromer. The objective for part B of the study was therefore met: patiromer treatment resulted in a continued maintenance of serum potassium within normal range, whereas the opposite was observed for placebo (i.e., no treatment), where serum potassium level increased with recurrence of hyperkalemia. Concordantly, secondary end points for part B demonstrated a higher proportion of placebo-treated patients had serum potassium levels of 5.1 mmol/L or greater compared with patiromer-treated patients after 8 weeks of treatment. Additional Kaplan–Meier analyses supported these findings: a higher proportion of placebo-treated patients had serum potassium of 5.1 mmol/L or greater, and 5.5 mmol/L or greater at the first study visit in part B compared with patiromer; the between-treatment difference increased with time. A comparison of recurrent hyperkalemia (defined as first occurrence of ≥ 5.5 mmol/L during the first 4 weeks of part B or ≥ 5.1 mmol/L during the second 4 weeks of part B) between the treatment groups suggested the placebo group had a higher rate of recurrence than the patiromer group within the first week, and the difference increased with time. Taken together, these results supported the objective of part B: patiromer resulted in maintaining serum potassium levels and prevented the recurrence of hyperkalemia.

As noted previously, it is important for patients with CKD to remain on optimized RAASi treatment to reduce the risk of adverse cardiovascular and kidney events. A number of exploratory outcomes were assessed in OPAL-HK to determine the pattern of RAASi dosing throughout the study. Approximately three-quarters of patients in the patiromer group did not require any dose adjustments (for either patiromer or an RAASi) to complete part B of the study, compared with one-third of patients on placebo. More than half of the patients in the placebo group had a reduction in dose or complete discontinuation of RAASi therapy to manage hyperkalemia. By the end of part B, more than 90% of patients receiving patiromer continued their RAASi medications compared with less than half of placebo-treated patients. While these analyses were considered exploratory, and no statistical comparison was done,

these results nonetheless suggest that patiromer allowed fewer hyperkalemic patients to discontinue or reduce the dose of their RAASi medications.

Notable strengths and weaknesses of the OPAL-HK trial include the following. The study had adequate power (> 90%), with results from subgroup and sensitivity analyses confirming findings of the primary efficacy analyses, well balanced baseline characteristics, and high compliance for those who completed the study (although the short trial length and restrictive selection of patients could have contributed to this). With respect to internal validity, the study had a moderate completion rate, despite consisting of a selective group of patients, a single-arm design and potential regression to the mean (in part A), and potential unblinding of patients due to the factors described previously (in part B) — all of which could bias the results in favour of patiromer. Three major concerns that limited the generalizability of the results include: the selection of patients based on a lack of any significant or interfering comorbidities (part A) and response to treatment (part B), the short duration of the trial (12 weeks), and the choice of serum potassium as the basis for all efficacy end points. While AMETHYST-DN provided longer-term efficacy and safety data, the effect of patiromer on clinical end points, such as major adverse cardiovascular events or major adverse kidney events, hospitalizations, mortality, and quality of life, is uncertain. It is unclear if the benefits in the management of serum potassium in the short-term would translate to clinical benefits over the long-term and prevent serious hyperkalemic events that could be fatal or require hospitalization. Additionally, patients initially included in the trial had mild to moderate levels of hyperkalemia (5.1 mmol/L to < 6.5 mmol/L). Those who responded to part A treatment and subsequently entered part B had serum potassium of less than 5.0 mmol/L, as required by design. Therefore, the extent to which patients with a moderate or severe level of hyperkalemia (> 6 mmol/L) would respond to continued patiromer treatment without being enriched by external factors is unclear. In response, the sponsor provided information from a pooled analysis of 3 clinical trials of patiromer (AMETHYST-DN and OPAL-HK, discussed here, as well as TOURMALINE, which did not meet the inclusion criteria for this review), that had a total of 53 out of 623 patients with baseline serum potassium of 6.0 mmol/L or greater. The pooled analysis showed a reduction of serum potassium by −1.67 mmol/L; the mean level was reduced to less than 5.5 mmol/L 48 hours after the first dose and the target range was reached in 93% of patients through 4 weeks. Notwithstanding the small proportion of patients with moderate hyperkalemia in the pooled analysis (53 out of 623 patients), it is difficult to draw conclusions from this information without a detailed methodology of data pooling, especially given the inherent heterogeneities across studies.

The AMETHYST-DN trial provided evidence for the longer-term efficacy and safety of patiromer (i.e., approximately 1 year) at doses ranging from 8.4 g/day to 33.6 g/day (which could be titrated up to 50.4 g/day). Across different dose groups, serum potassium levels reduced from baseline to week 4 and through the end of the treatment period. Similar to the findings from OPAL-HK, there was a larger reduction of serum potassium in patients with higher (> 5.5 mmol/L to < 6.0 mmol/L) baseline potassium levels than in those with lower baseline potassium levels (> 5.0 mmol/L to 5.5 mmol/L). The mean reduction of serum potassium was similar in each stratum, regardless of the initiation dose, indicating that the initiation dose of patiromer does not appear to have a dose-response effect, which is also supported by the dosing-finding study. More than 95% of the patients reached the target range (3.8 mmol/L to 5.0 mmol/L) during the 8-week TIP and maintained target levels during the LTMP for approximately 80% of the time.

Taken together, these 2 trials support the potassium-lowering effect of patiromer, both short and long-term.

Harms

Few patients reported SAEs throughout the OPAL-HK trial and there was 1 death that was not likely related to patiromer. Almost half of the patients experienced 1 or more AEs, although most occurred at a frequency of 5% or less. The occurrence of notable AEs, such as hypomagnesemia or hypokalemia were rare, and no major GI adverse effects (e.g., intestinal perforation) were reported.

However, as mentioned, controlled trial data informing the safety of patiromer are limited to 12 weeks of study. The longer-term AMTHYST-DN phase II study provides additional safety data but, without comparison with placebo or another active treatment of hyperkalemia, this makes the results difficult to interpret. The Health Canada safety evaluation focused on a pooled analysis conducted by the sponsor of safety data from 4 trials, including Study 301 (OPAL-HK), Study 205 (AMETHYST-DN), Study 202, and Study 204. Studies 202 and 204 were phase II trials that did not meet the inclusion criteria of this systematic review, as they both included normokalemic patients (4.3 mmol/L to 5.1 mmol/L) and were aimed at assessing the efficacy and safety of patiromer for the prevention of hyperkalemia when initiating spironolactone.

In the pooled safety population of 666 patients, a total of 60.8% of patients reported at least 1 AE. Withdrawals due to AEs were reported by a total of 9% of patients. Overall, the most common AEs (> 5%) were constipation (7.2%), chronic renal failure (5.4%), hypomagnesemia (5.3%), and mild to moderate hypokalemia (< 3.5 mmol/L, in the patiromer group only) (4.7%). In addition, diarrhea, hypertension, hypokalemia, anemia, headache, nausea, hyperglycemia, abdominal discomfort, flatulence, hypoglycemia, peripheral edema, and ventricular or supraventricular extrasystoles occurred at a frequency of 2% or greater (up to a maximum of 10%); these AEs were mild to moderate in nature. The sponsor provided an analysis of AEs by patiromer dose, although the data were confounded by dose titrations, different treatment durations, and comorbidities. Therefore, Health Canada was unable to draw any conclusions on whether there was a dose-response relationship between dosage and AE frequency.

SAEs occurred in 8.3% of the pooled safety population. Cardiac disorders were the most common class of SAEs (2.4%), although no individual SAE was reported in 2% or more of patients. Importantly, there were no SAEs related to hypokalemia, hypomagnesemia, or other notable AEs of interest that would be expected to be related to patiromer, although there were 2 incidences of GI perforation in the AMETHYST-DN trial.

Across the 4 trials, 18 patients treated with patiromer died. Health Canada could not establish a clear temporal pattern associated with these deaths. Fifteen of these deaths were adjudicated as cardiovascular in etiology, with none likely to be related to hypo- or hyperkalemia. None of the patients who died had a final serum potassium value of less than 3.5 mmol/L or a final serum magnesium value of less than 1.4 mg/dL. The major risk factors for death included age (≥ 65 years), male sex, CKD, diabetes, heart failure, hypertension, and prior myocardial infarction. Given the non-absorbed nature of patiromer, and the numerous underlying comorbidities and risk factors for death among the patients who died, Health Canada concluded that the deaths were not expected to be related to patiromer.

Overall, there are little data to indicate that patiromer is clearly associated with SAEs. There are insufficient data, however, to fully inform on the longer-term balance of benefit to harms with patiromer.

Conclusions

The efficacy and safety of patiromer was assessed in a 12-week single-blind, phase III trial, with supportive evidence provided by an open-label, dose-ranging, phase II trial with 1 year of follow-up data. Based on evidence from the phase III trial, 4 weeks of patiromer treatment at 8.4 g/day and 16.8 g/day reduced serum potassium to a clinically meaningful level among hyperkalemic patients (baseline serum potassium between 5.1 mmol/L and 6.5 mmol/L) who had CKD (baseline eGFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2) and were on RAASi treatment. More than 70% of these patients achieved a normal level of serum potassium (3.8 mmol/L to < 5.1 mmol/L). Further continuation of patiromer for 8 weeks resulted in the maintenance of normal serum potassium in these patients, whereas withdrawal from patiromer led to a recurrence of hyperkalemia. A large proportion of patients were able to continue patiromer and RAASi treatment (94%), of which only 6% required RAASi dose modification or discontinuation. The biggest limitation of the trial was the use of highly restrictive criteria for enrolling patients, who were selected based on an absence of significant or unstable comorbidities (other than CKD and manageable diabetes and heart conditions), as well as their response to patiromer treatment. The effects observed may therefore not be generalizable to the larger population of patients. Additionally, the effects were observed primarily in mildly hyperkalemic patients; therefore, it is unclear whether patients with moderate or severe hyperkalemia (serum potassium > 6.0 mmol/L) would respond to patiromer to the same extent. It is also uncertain whether controlling serum potassium would translate into clinical benefits, notably preventing major cardiac or kidney events and hospitalizations. Few AEs and SAEs were reported, although the short duration of the trial and selection of patients who showed response to treatment limited the ability to detect any safety signal with confidence. Nonetheless, safety data from the longer-term, phase II trial and the Health Canada safety evaluation also did not identify clear safety concerns. Most AEs were GI-related, as expected from a potassium binder. There were no direct or indirect comparisons of patiromer with other potassium binders or treatments for hyperkalemia, and placebo is unlikely to be the best comparator; therefore, the comparative benefit and safety of this medication is unknown. Overall, patiromer appears to be effective in reducing serum potassium in patients with mild hyperkalemia and CKD and has no major safety concerns; however, its effect on clinical end points in less certain, particularly among patients with moderate or severe hyperkalemia.

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Appendix 1: Literature Search Strategy

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946–present)
- Embase (1974–present)
- **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: November 27, 2020

Alerts: Bi-weekly search updates until project completion

Study types: All study types

Limits: Conference abstracts: excluded

Table 29: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.dq.	Candidate term word
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm.	Name of substance word
.ot.	Original title
.pt	Publication type
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Database(s): Embase 1974 to 2020 November 26, Ovid MEDLINE(R) ALL 1946 to November 26, 2020

Search strategy:

1. (Veltassa* or patiromer* or patiromir* or RLY 5016* or RLY5016* or 1FQ2RY5YHH or 0LB9J2797D or 7T97I3787N).ti,ab,ot,kf,hw,nm,rn.
2. 1 use medall
3. *Patiromer/ or (Veltassa* or patiromer* or patiromir* or RLY 5016* or RLY5016*).ti,ab,kw,dq.
4. 3 use oemezd
5. 4 not (conference abstract or conference review).pt.
6. 2 or 5
7. remove duplicates from 6

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search – Studies with results | Veltassa OR patiromer]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms – Veltassa, patiromer]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms – Veltassa, patiromer]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms – Veltassa, patiromer]

Other Databases

Cochrane Central Register of Controlled Trials

Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.

Grey Literature

Search dates: November 17 to 20, 2020

Keywords: Veltassa, patiromer, hyperkalemia, hyperkalaemia

Limits: No limits

Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)

Appendix 2: Excluded Studies

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 30: Excluded Studies

Reference	Reason for exclusion
Agarwal et al. (2018)[22]	Study population
Agarwal et al. (2019)[23]	Study population
Buysse et al. (2012)[24]	Study population

Appendix 3: Detailed Outcome Data

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 31: Subgroup Analyses for Primary Efficacy Outcome — Part A

Subgroup	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 90	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 147	Total 5.1 mmol/L to < 6.5 mmol/L N = 237
Change in serum K^+, mmol/L			
Type 2 diabetes mellitus			
Present, n	52	86	138
Mean ± SE (95% CI)	−0.65 ± 0.066 (−0.78 to −0.52)	−1.22 ± 0.051 (−1.32 to −1.12)	−1.00 ± 0.040 (−1.08 to −0.92)
P value	—	—	< 0.001
Not present, n	38	61	99
Mean ± SE (95% CI)	−0.62 ± 0.078 (−0.78 to −0.47)	−1.26 ± 0.063 (−1.39 to −1.13)	−1.02 ± 0.051 (−1.12 to −0.92)
P value	—	—	< 0.001
Interaction P value	—	—	0.77
Heart failure			
Present, n	38	62	100
Mean ± SE (95% CI)	−0.74 ± 0.083 (−0.91 to −0.57)	−1.26 ± 0.068 (−1.40 to −1.12)	−1.06 ± 0.052 (−1.16 to −0.95)
P value	—	—	< 0.001
Not present, n	52	85	137
Mean ± SE (95% CI)	−0.57 ± 0.055 (−0.67 to −0.46)	−1.24 ± 0.049 (−1.34 to −1.14)	−0.98 ± 0.039 (−1.06 to −0.90)
P value	—	—	< 0.001
Interaction P value	—	—	0.22
RAASi			
On maximal dose, n	41	61	102
Mean ± SE (95% CI)	−0.66 ± 0.068 (−0.80 to −0.52)	−1.18 ± 0.059 (−1.29 to −1.06)	−0.96 ± 0.045 (−1.05 to −0.87)
P value	—	—	< 0.001
Not on maximal dose, n	49	86	135
Mean ± SE (95% CI)	−0.64 ± 0.071 (−0.79 to −0.50)	−1.28 ± 0.053 (−1.38 to −1.17)	−1.05 ± 0.044 (−1.13 to −0.96)
P value	—	—	< 0.001

Subgroup	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 90	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 147	Total 5.1 mmol/L to < 6.5 mmol/L N = 237
Interaction P value	—	—	0.20

CI = confidence interval; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor; SE = standard error.

Source: OPAL-HK Clinical Study Report.[8]

Table 32: Subgroup Analyses for Secondary Efficacy Outcome — Part A

Subgroup	Dose group 1 5.1 mmol/L to < 5.5 mmol/L N = 90	Dose group 2 5.5 mmol/L to < 6.5 mmol/L N = 147	Total 5.1 mmol/L to < 6.5 mmol/L N = 237
Patients who achieved success (i.e., serum K^+ in the target range of 3.8 mmol/L to < 5.1 mmol/L) at week 4			
Type 2 diabetes mellitus			
Present, n (%)	52 (57)	87 (58)	139 (57)
Percentage (95% CI)	77 (66 to 88)	78 (70 to 86)	78 (71 to 84)
Not present, n (%)	40 (43)	64 (42)	104 (43)
Percentage (95% CI)	70 (57 to 83)	75 (65 to 85)	73 (65 to 81)
Interaction P value			0.42
Heart failure			
Present, n (%)	39 (42)	63 (42)	102 (42)
Percentage (95% CI)	74 (61 to 87)	78 (68 to 87)	76 (69 to 84)
Not present, n (%)	53 (58)	88 (58)	141 (58)
Percentage (95% CI)	74 (62 to 85)	76 (67 to 85)	75 (68 to 82)
Interaction P value			0.78
RAASi			
On maximal dose, n (%)	42 (46)	64 (42)	106 (44)
Percentage (95% CI)	74 (62 to 85)	78 (69 to 87)	76 (69 to 84)
Not on maximal dose, n (%)	50 (54)	87 (58)	137 (56)
Percentage (95% CI)	74 (62 to 86)	76 (67 to 84)	75 (68 to 82)
Interaction P value			0.73

CI = confidence interval; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor; SE = standard error.
Source: OPAL-HK Clinical Study Report.[8]

Table 33: Subgroup Analyses for Primary Efficacy Outcome — Part B

Subgroup	Placebo N = 52	Patiromer N = 55
Change in serum K^+ from part B baseline to part B week 4 or the first target serum K^+ range of < 3.8 mmol/L or ≥ 5.5 mmol/L		
Type 2 diabetes mellitus		
Present, n (%)	67 (63)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.69 (0.19 to 1.29)	0.03 (−0.20 to 0.30)
Difference in median change, estimates (95% CI)	0.66 (0.28 to 1.03)	
P value	< 0.001	
Not present, n (%)	40 (37)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.72 (0.32 to 1.22)	−0.10 (−0.30 to 0.35)
Difference in median change, estimates (95% CI)	0.82 (0.47 to 1.17)	
P value	< 0.001	
Interaction P value	0.56	
Heart failure		
Present, n (%)	49 (46)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.74 (0.44 to 1.04)	0.10 (−0.30 to 0.30)
Difference in median change, estimates (95% CI)	0.64 (0.29 to 0.99)	
P value	< 0.001	
Not present, n (%)	58 (54)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.78 (0.08 to 1.23)	−0.05 (−0.25 to 0.30)
Difference in median change, estimates (95% CI)	0.83 (0.42 to 1.24)	
P value	< 0.001	
Interaction P value	0.50	
Baseline serum K^+		
< 5.8 mmol/L, n (%)	53 (50)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.80 (0.10 to 1.20)	0.00 (−0.20 to 0.40)
Difference in median change, estimates (95% CI)	0.80 (0.44 to 1.17)	
P value	< 0.001	
≥ 5.8 mmol/L, n (%)	54 (50)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.72 (0.47 to 1.47)	0.00 (−0.39 to 0.25)

Subgroup	Placebo N = 52	Patiromer N = 55
Difference in median change, estimates (95% CI)	0.72 (0.34 to 1.09)	
P value	< 0.001	
Interaction P value	0.74	
RAASi		
On maximal dose, n (%)	42 (39)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.82 (0.62 to 1.55)	−0.10 (−0.30 to 0.20)
Difference in median change, estimates (95% CI)	0.92 (0.54 to 1.29)	
P value	< 0.001	
Not on maximal dose, n (%)	65 (61)	
Estimated change in serum K^+ from part B baseline to part B week 4 to median (quartiles)	0.79 (0.29 to 1.39)	0.10 (−0.20 to 0.30)
Difference in median change, estimates (95% CI)	0.69 (0.32 to 1.05)	
P value	< 0.001	
Interaction P value	0.41	

CI = confidence interval; ITT = intention to treat; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.
Source: OPAL-HK Clinical Study Report.[8]

Table 34: Subgroup Analyses of Secondary Outcomes — Part B

Secondary outcomes	Placebo N = 52	Patiromer N = 55
Number of patients with a serum K^+ value ≥ 5.5 mmol/L at any time through part B (week 8)		
Type 2 diabetes mellitus		
Present, n (%)	33 (63)	34 (62)
Percentages (95% CI)	62 (43 to 78)	19 (7 to 36)
Difference in treatment groups, estimates (95% CI)	43 (22 to 64)	
P value	< 0.001	
Not present, n (%)	19 (37)	21 (38)
Percentages (95% CI)	58 (33 to 80)	10 (1 to 31)
Difference in treatment groups, estimates (95% CI)	48 (22 to 73)	
P value	< 0.001	
Interaction P value	0.77	
Heart failure		
Present, n (%)	22 (42)	27 (49)
Percentages (95% CI)	52 (30 to 74)	8 (1 to 25)
Difference in treatment groups, estimates (95% CI)	46 (24 to 69)	
P value	< 0.001	
Not present, n (%)	30 (58)	28 (51)
Percentages (95% CI)	66 (47 to 82)	23 (9 to 42)
Difference in treatment groups, estimates (95% CI)	47 (25 to 69)	
P value	< 0.001	
Interaction P value	0.96	
Baseline serum K^+		
< 5.8 mmol/L, n (%)	26 (50)	27 (49)
Percentages (95% CI)	57 (36 to 76)	20 (7 to 39)
Difference in treatment groups, estimates (95% CI)	37 (13 to 61)	
P value	0.003	
≥ 5.8 mmol/L, n (%)	26 (50)	28 (51)
Percentages (95% CI)	63 (42 to 81)	11 (2 to 29)
Difference in treatment groups, estimates (95% CI)	52 (30 to 74)	
P value	< 0.001	
Interaction P value	0.35	
RAASi		

Secondary outcomes	Placebo N = 52	Patiromer N = 55
On maximal dose, n (%)	21 (40)	21 (38)
Percentages (95% CI)	59 (35 to 79)	21 (7 to 44)
Difference in treatment groups, estimates (95% CI)	38 (12 to 63)	
P value	0.003	
Not on maximal dose, n (%)	31 (60)	34 (62)
Percentages (95% CI)	61 (42 to 78)	12 (3 to 27)
Difference in treatment groups, estimates (95% CI)	49 (29 to 69)	
P value	< 0.001	
Interaction P value	0.48	
Subgroup analysis (percentage of patients with a serum K^+ value ≥ 5.1 mmol/L at any time through part B week 8)		
Type 2 diabetes mellitus		
Present, n (%)	33 (63)	34 (62)
Percentages (95% CI)	89 (73 to 97)	41 (25 to 59)
Difference in treatment groups, estimates (95% CI)	48 (28 to 68)	
P value	< 0.001	
Not present, n (%)	19 (37)	21 (38)
Percentages (95% CI)	95 (74 to > 99)	46 (25 to 69)
Difference in treatment groups, estimates (95% CI)	48 (25 to 72)	
P value	< 0.001	
Interaction P value	0.96	
Heart failure		
Present, n (%)	22 (42)	27 (49)
Percentages (95% CI)	95 (77 to > 99)	36 (19 to 57)
Difference in treatment groups, estimates (95% CI)	59 (41 to 77)	
P value	< 0.001	
Not present, n (%)	30 (58)	28 (51)
Percentages (95% CI)	88 (71 to 97)	50 (31 to 69)
Difference in treatment groups, estimates (95% CI)	38 (16 to 60)	
P value	0.001	
Interaction P value	0.15	
Baseline serum K		
< 5.8 mmol/L, n (%)	26 (50)	27 (49)
Percentages (95% CI)	86 (67 to 96)	48 (28 to 68)
difference in treatment groups, estimates (95% CI)	38 (14 to 62)	

Secondary outcomes	Placebo N = 52	Patiromer N = 55
P value	0.002	
≥ 5.8 mmol/L, n (%)	26 (50)	28 (51)
Percentages (95% CI)	96 (80 to > 99)	39 (21 to 59)
Difference in treatment groups, estimates (95% CI)	58 (39 to 77)	
P value	< 0.001	
Interaction P value	0.20	
RAASi		
On maximal dose, n (%)	21 (40)	21 (38)
Percentages (95% CI)	95 (76 to > 99)	50 (28 to 72)
Difference in treatment groups, estimates (95% CI)	45 (25 to 66)	
P value	< 0.001	
Not on maximal dose, n (%)	31 (60)	34 (62)
Percentages (95% CI)	88 (72 to 97)	39 (23 to 57)
Difference in treatment groups, estimates (95% CI)	50 (30 to 69)	
P value	< 0.001	
Interaction P value	0.77	

CI = confidence interval; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: OPAL-HK Clinical Study Report.[8]

CADTH

Pharmacoeconomic Review

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
CKD	chronic kidney disease
CV	cardiovascular
eGFR	estimated glomerular filtration rate
ICER	incremental cost-effectiveness ratio
NMA	network meta-analysis
QALY	quality-adjusted life-year
RAASi	renin-angiotensin-aldosterone system inhibitor

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Conclusions

The sponsor's base case included several assumptions that were not substantiated by quality evidence and were based on surrogate outcomes measured in OPAL-HK, both of which are likely to favour patiromer. First, the sponsor assumed that acute hospitalizations in the 6 months after hyperkalemia can be attributed to hyperkalemia and can be reduced by treating with patiromer; however, this assumption is not supported by reasonable quality evidence. When this assumption is removed, patiromer is no longer a cost saving, underscoring the significant impact of the assumption on the results. Second, the average dose of patiromer in the trial was 21 g, indicating that a proportion of patients required 2 sachets, increasing daily costs. Third, while it is plausible that management of hyperkalemia with patiromer may allow more patients to be treated with a renin-angiotensin-aldosterone system inhibitor (RAASi), there is significant uncertainty regarding the magnitude of this effect on health outcomes.

Combining these 3 factors in the CADTH base case, the incremental cost-effectiveness ratio (ICER) of patiromer plus current practice relative to current practice alone is $475,196 per quality-adjusted life-year (QALY). An 85% price reduction is required to have an ICER less than $50,000 per QALY.

The sponsor also assumed significant discontinuation of patiromer over time. If long-term use of patiromer is assumed, the ICER increases to over $4 million per QALY, and a 99% price reduction is needed to achieve an ICER of $50,000 per QALY. However, significant uncertainty remains, and a greater price reduction would be required if a larger proportion of patients take the maximum dose of patiromer or there is a lower assumed benefit associated with RAASi use.

Table 1: Submitted for Review

Item	Description
Drug product	Patiromer powder for oral suspension (Veltassa), 8.4 g or 16.8 g
Submitted price	$9.80 per 8.4 g or 16.8 g sachet
Indication	Treatment of hyperkalemia in adults with chronic kidney disease (estimated glomerular filtration rate [eGFR]) ≥ 15 mL/min/1.73 m^2)
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	October 3, 2018
Reimbursement request	For the treatment of hyperkalemia in patients with CKD 3 to 4 on RAASi therapy
Sponsor	Otsuka Canada Pharmaceutical
Submission history	Previously reviewed: No

CKD = chronic kidney disease; NOC = Notice of Compliance; RAASi = renin-angiotensin-aldosterone system inhibitors.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	• Cost-utility analysis • Markov model
Target populations	Patients with CKD stage 3 and 4 on RAASi with HK (serum potassium concentration ≥ 5.5 mmol/L)
Treatment	Patiromer (plus current practice)
Comparator	Current practice (RAASi down-titration or discontinuation and loop diuretic use)
Perspective	Canadian publicly funded health care payer
Outcome	• Life-years • QALYs
Time horizon	Lifetime (35 years)
Key data source	• OPAL-HK study • Clinical Practice Research Datalink network meta-analysis (Xie et al. [2016])
Submitted results for base case	Relative to current practice alone, patiromer plus current practice was dominant (cost less and more effective), producing 0.01749 more QALYs at a cost saving of $1,239 per patient over 35 years. Key scenario analyses: • Using discontinuation data for patiromer from a US claims data analysis, patiromer plus current practice remained dominant. • In patients with stage 3 to stage 4 CKD with a serum potassium of > 6.0 mmol/L at baseline on RAASi, patiromer plus current practice remained dominant.
Key limitations	• The sponsor assumed increased all-cause acute hospitalization for 6 months for patients experiencing HK, based on a Danish observational study. Hospitalization due to HK was not measured within the trial, nor was the assumption that treatment with patiromer would reduce acute all-cause hospitalization over a subsequent 6-month period. • The OPAL-HK trial was 12 weeks long, with serum potassium measured as a surrogate outcome. All health benefits in the economic model were mediated through the benefits of RAASi use, with the assumption that management of HK will result in greater RAASi use, which in turn would improve health. There is significant uncertainty regarding the relationship between serum potassium levels and RAASi use and, likewise, the health consequences of increased RAASi use. Neither of these outcomes was explored in the clinical trial. • The sponsor assumed the daily use of 1 sachet (8.4 g or 16.8 g per day, flat price). However, OPAL-HK reported a mean daily dose of 21 g, indicating a significant proportion of patients would be on a dose greater than 16.8 g per day, with twice the daily cost. • Discontinuation was estimated from an exponential curve based on OPAL-HK data over 8 weeks for patiromer. In the clinical trial, actual use was 81% after 8 weeks, but modelled to be 30% at 1 year and no use at 4.5 years. According to the CADTH clinical expert, in those patients who initially tolerate patiromer, it is likely to be used long-term, if approved.
CADTH reanalysis results	• In the CADTH base case, the ICER of patiromer plus current practice relative to current practice alone was $475,196 per QALY. • A price reduction of approximately 85% is required to have an ICER of less than $50,000 per QALY. • A greater price reduction would be required if there is no discontinuation of patiromer, more patients use the maximum dose, and/or the benefit of RAASi is lower.

CKD = chronic kidney disease; HK = hyperkalemia; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RAASi = renin-angiotensin-aldosterone system inhibitor.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input was received from the Kidney Foundation of Canada, which collected patient input in October and November of 2020 through self-administered questionnaires. Chronic kidney disease (CKD) is often associated with other medical conditions such as diabetes, high blood pressure, and heart disease. Many patients also emphasized the fatigue and sleep difficulties associated with CKD. Factors that were noted as "very important" or "important" when choosing CKD medications were: fatigue, interference with sleep and other medications, edema of the foot, effect on mood, changes in appetite, cost, and length of time on the medication. Three patients had experience with patiromer sorbitex calcium, with 2 reporting their potassium levels had improved from their levels before taking the medication. Among the 3 respondents, there were differing reports on the effect of patiromer on tiredness or weakness, nausea or vomiting, trouble breathing, swelling and edema, and palpitations or irregular heartbeat, with some participants indicating improvement of these symptoms and others indicating worsening of these symptoms.

Clinician input was received from 1 individual clinician at Sunnybrook Hospital and 1 group clinician input on behalf of 10 clinicians at the Scarborough Regional Nephrology Program. Clinicians noted a lack of efficacy of current treatments such as Kayexalate and also that it was "highly unpleasant." Clinicians noted that the current treatment paradigm is not evidence-based, and it is expected that patiromer will result in safer treatment. Patiromer would be most appropriate for patients with chronic disease who cannot be appropriately dosed with angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists due to their hyperkalemia.

Input from the drug plans noted there should be a clear definition of RAASi therapy for determining eligibility. The input also raised concerns about the number of patients who would be on the maximum dose of patiromer and would, therefore, require 2 packets to get the full dose. Finally, drug plans noted that the reimbursement request is narrower than the Health Canada indication, and that jurisdictions would likely get requests outside of the reimbursement request.

Some of these concerns were addressed in the sponsor's model:

- Side effects of patiromer, which is one of the important factors of CKD medication, were considered in the first 2 cycles of the model. Patients were assumed to discontinue patiromer once side effects occurred.

In addition, CADTH addressed some of these concerns, as follows:

- CADTH increased the proportion of patients expected to receive the highest dose of patiromer in the pharmacoeconomic model and the budget impact analysis.
- CADTH increased the estimate of the number of patients on RAASi therapy as part of a scenario analysis in the budget impact analysis.

CADTH was unable to address the following concerns raised from stakeholder input:

- The reimbursement request is narrower than the full Health Canada indication.

Economic Review

The current review is for patiromer (Veltassa) for patients with stage 3 to 4 CKD with a serum potassium of 5.5 mmol/L or greater at baseline on RAASi.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing patiromer plus current practice with current practice (RAASi down-titration or discontinuation and loop diuretic use) for patients with stage 3 to 4 CKD with a serum potassium of 5.5 mmol/L or greater at baseline on RAASi. This is narrower than the Health Canada indication for all CKD adults with an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m^2 or greater, which does not specify CKD stage or RAASI treatment.

The recommended starting dose is 8.4 g patiromer once daily. The daily dose may be adjusted by 8.4 g at intervals of 1 week or longer based on serum potassium level and the desired target range, up to a maximum of 25.2 g per day. Patiromer is available as individual sachets containing 8.4 g or 16.8 g of patiromer sorbitex calcium powder for oral suspension. The cost of patiromer is $9.80 per sachet, regardless of strength.

The analyses were conducted from the Canadian public payer perspective. The time horizon in the base case was 35 years to capture the maximum lifetime of patients with a modelled starting age of 65, with a 1.5% annual discount rate for costs and effects.

Model Structure

A Markov model structure (Figure 1 in Appendix 3) was used to model the outcomes associated with hyperkalemia and to capture the costs and effects associated with patiromer plus current practice versus current practice alone. The model incorporated 26 health states with a monthly cycle without half-cycle correction.

Each CKD stage (3 or 4) was split into 9 health states related to the patient's serum potassium level (< 5.5 mmol/L, 5.5 mmol/L to 6.0 mmol/L, and > 6.0 mmol/L), and whether they had experienced a cardiac event (no event, cardiovascular [CV] event, post-CV event). If the patient's serum potassium level was less than 5.5 mmol/L, it was assumed they would receive a full RAASi dose. If the patient's serum potassium level was 5.5 mmol/L to 6.0 mmol/L, they would receive a reduced dose (50% of full dose). If the patient's serum potassium level rose above 6.0 mmol/L, then they would discontinue their RAASi. Patients could also progress sequentially through CKD stages to end-stage kidney disease (ESKD) and could experience death from any of the health states. Patients started in the following 4 health states:

- CKD stage 3 with serum potassium of 5.5 mmol/L to 6.0 mmol/L
- CKD stage 3 with serum potassium greater than 6.0 mmol/L
- CKD stage 4 with serum potassium of 5.5 mmol/L to 6.0 mmol/L
- CKD stage 4 with serum potassium greater than 6.0 mmol/L.

Patients could then transition between serum potassium level categories and progress through CKD stages (stage 3 to stage 4 and stage 4 to end-stage renal disease [ESRD]).

At any point, they could experience a cardiac event and either die or move to the post-CV event stage.

Model Inputs

In the base case, the patients' baseline characteristics were obtained from the OPAL-HK trial. The OPAL-HK trial was a phase III, single-blind, 2-phase trial where the first phase (part A) was a single-arm treatment phase followed by a randomized, placebo-controlled withdrawal phase (part B). At model entry, the distribution of patients into the 4 starting health states in both arms was informed by patient-level data from baseline of part A of OPAL-HK. Initial transition probabilities from the starting health states for the patiromer arm were informed by OPAL-HK part B, while the transition probabilities for the current practice arm were informed by the Clinical Practice Research Datalink (CPRD) database from the UK. In the second cycle, transition probabilities in the current practice arm were informed by the CPRD database, and the transition probabilities of serum potassium rising from less than 5.1 mmol/L to 5.5 mmol/L or greater for the patiromer arm were modelled by applying a hazard ratio (HR) of 0.1268, estimated from OPAL-HK part B. The HR was adjusted in each cycle according to the proportion of patients on patiromer. The HR for developing hyperkalemia was applied for the entire duration that a patient remained on patiromer.

Probabilities related to CV events, CV death, and CKD progression were derived from a network meta-analysis (NMA) conducted by Xie et al.[1] that compared the effects of ACEi or ARB against placebo among patients with CKD. The probability of experiencing a CV event or CKD progression in the "discontinued RAASi" health state was obtained from the placebo arm of the NMA and adjusted based on the ratio of ACEi and ARB use from the CPRD analysis. For the "full RAASi" health state, CV event and CKD progression were derived by applying the odds ratio (OR) from the NMA to the probabilities of the placebo arm. Lastly, CV event and CKD progression for the "reduced RAASi" health state were estimated to be half of the treatment arm from the NMA (assumed 50% baseline risks from RAASi and 50% baseline risk from placebo). It was also assumed that transition probabilities in both the patiromer and current practice arms were unaffected by the occurrence of CV events.

Discontinuation of patiromer was estimated by fitting an exponential curve from the OPAL-HK trial part B (8 weeks) to inform the proportion of patients discontinuing in each cycle. Observed patiromer use after 8 weeks was 82%; 30% of patients were estimated to remain on patiromer after 1 year. A treatment discontinuation curve extrapolated from US real-world data was explored in the scenario analysis. It was also assumed that if the adverse events (AEs) were severe enough to result in management costs and AE-related disutility, patients would discontinue therapy. Therefore, AEs were considered only in the first and second cycles.

Other clinical inputs, such as the proportion of dialysis and transplant used to inform ESKD costs, were obtained from the Canadian Organ Replacement Register. The proportion of patients in the CV event state who experienced a myocardial infarction (MI) or stroke were informed from a UK financial study.[2] Life tables informing general population mortality were informed by Statistics Canada. Standardized mortality ratios for age and CKD stages were obtained from 2 Norwegian and Canadian studies.[3,4]

Utility values associated with CKD stages and ESRD were informed by a UK study.[5] Utility values related to CV events and post-CV events were also obtained from another UK study,[6] where the average of the utility values for MI and stroke were used in the model based on the ratio from Kerr (2012). It was assumed that hyperkalemia itself would not incur a utility

decrement. A baseline utility, based on age and sex, was obtained from a UK study and was applied to the first cycle.[7] Utility decrements due to AEs, such as constipation, diarrhea, and nausea, were obtained from published literature and applied only to the first and second cycles.[8-10]

The dosing schedule of patiromer was assumed to be 8.4 mg daily in the model, based on the Canadian product monograph. The cost is $9.80 per packet regardless of dose, with an annual cost of $3,579.45. The sponsor claimed the 25.2 g dosage was not accounted for in the model, as this formulation is not available in Canada and data from the US suggest that an estimated 1% of patients are prescribed this dosage. Current practice was assumed to incur no treatment costs, as standard treatments such as loop diuretics were assumed to be used equally in both arms. A prescribing cost was also added to patiromer, assuming a 10-minute general practitioner appointment 2 times a year ($16.89 × 2), and a dispensing fee of $9.93 four times annually, with a total annual prescribing cost of $73.50.

CKD health state costs, including primary care costs, nephrologist costs, and inpatient costs, were obtained from the Ontario Schedule of Benefits, Government of Canada Job Bank, and Ontario Case Costing Initiative (OCCI). ESRD health state costs included a weighted average cost for peritoneal dialysis, hemodialysis, and kidney transplant from 2 costing studies in Manitoba and Alberta.[11,12] CKD medications (annual cost of $57.01), including a calcium channel blocker and a loop diuretic, were also added. CV health state costs were calculated as a weighted average between the cost of MI and a stoke obtained from OCCI. Post-CV event health state costs were assumed to be the same as the general CKD population plus the cost of concomitant medication (75 mg clopidogrel once per day, with an annual cost of $96.03).

The rate of hospitalization associated with hyperkalemia was derived from a Danish population–based matched cohort study.[13] The increase in mean acute hospitalization per patient was 0.52 to 0.62 within 6 months of hyperkalemia, which translates to a monthly probability increase of 4.5% to 9.1%, and was applied to patients in the model for 6 months after hyperkalemia (defined as an increase to either 5.5 mmol/L to 6.0 mmol/L or > 6.0 mmol/L). The cost of a standard hospital stay was applied ($6,268.75).

The cost of RAASi medications was estimated by taking a weighted average for ACEi and ARB, based on the proportion of patients reported in a Canadian cost-effectiveness study on CKD patients.[14] The cost of RAASi was 50% less in the mid serum potassium health state (5.5 mmol/L to 6.0 mmol/L), as partial dosing was assumed, while the cost of RAASi was $0 due to non-use in the health state with potassium greater than 6.0 mmol/L. The costs of managing AEs was assumed to arise solely from the costs of medications (ranged from $4.77 to $10.50 per event) and assumed to not require hospitalization or additional physician consultations. All medication costs were obtained from the Ontario Drug Benefit formulary.

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 1,000 probabilistic iterations, for which findings are presented subsequently.

Base-Case Results

In the sponsor's base-case analysis, patiromer (plus current practice; patiromer hereafter) was dominant compared with current practice (e.g., less costly and more effective). Specifically, patiromer was associated with 0.01749 additional QALYs and $1,239 lower costs compared with current practice over a 35-year modelled time horizon. (Disaggregated results

are presented in Table 10 and Table 11 in Appendix 3). The cost-effectiveness acceptability curves found that 100% of the results were cost-effective, regardless of the willingness-to-pay threshold (Figure 2 in Appendix 3). The results of the deterministic analysis were similar to the results of the probabilistic analysis.

Most of the incremental cost was attributable to the higher drug costs with patiromer, with cost savings associated with lower CKD health state costs due to fewer hyperkalemia-related hospitalizations (Table 10). The major driver contributing to QALY gains for patiromer was from the CKD stage 3 health state (Table 11).

Sensitivity and Scenario Analysis Results

Uncertainty was addressed probabilistically by exploring alternative health state utility values, US real-world data discontinuation, alternative hyperkalemia hospitalization cost, the population greater than 6.0 mmol/L only, a 15-year time horizon, and 0% to 3% discount rates. Patiromer remained the dominant strategy in all of the sponsor's sensitivity and scenario analyses.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations with the sponsor's analysis that have notable implications on the economic analysis:

- **Assumed increased hospitalization for hyperkalemia.** The model assumed increased acute hospitalization for patients with hyperkalemia (monthly probability of 4% or 9%, depending on serum potassium level of either > 5.5 mmol/L to 6.0 mmol/L or > 6.0 mmol/L) over a 6-month period after development of hyperkalemia based on a Danish observational study. The cause of hospitalization was not reported in the economic analysis, causation (versus association) with hyperkalemia was not established, nor was it reported in the clinical trial that treating hyperkalemia with patiromer would reduce all-cause acute hospitalization. The hospitalization event does not appear to be related to acute management of hyperkalemia, which can often be done as an outpatient, with only very severe cases requiring management in the emergency room, according to the CADTH clinical expert. As such, any change in subsequent all-cause acute hospitalization related to hyperkalemia and its treatment is speculative.
    - CADTH assumed no difference in hospitalization for hyperkalemia by treatment arm (by setting hyperkalemia hospitalization cost to $0).
- **Short trial duration and surrogate end point.** The OPAL-HK trial was 12 weeks long (4-week single-arm part A and 8-week placebo-controlled part B), with serum potassium measured as a surrogate outcome. All health benefits in the economic model were mediated through the benefits of RAASi, with the assumption that management

Table 3: Summary of the Sponsor's Economic Evaluation Results

Economic evaluation results	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALY)
Patiromer (plus current practice)	137,172	−1,239	6.189	0.01749	Dominant
Current practice	138,411	—	6.168	—	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[15]

of hyperkalemia with patiromer will result in greater RAASi use. There are several uncertainties regarding this within the economic analysis.

First, the extrapolation of trial results of reduced serum potassium is highly uncertain. As dietary restriction of potassium may attenuate if patients are on patiromer, the impact of patiromer on potassium levels may lessen over time (with the subsequent attenuation of benefit attributed to increased RAASi use).

Second, the estimated association of serum potassium achieved and RAASi usage is highly uncertain. Real-world use of RAASi in the setting of hyperkalemia and patiromer is not known.

Finally, the attribution of benefits of RAASi from the NMA is also uncertain. The benefits of RAASi were taken from an NMA comparing RAASi with placebo; however, patients in the RAASi treatment arm in these studies would also experience dose-limiting hyperkalemia (leading to dose reduction or cessation). In a few of the major trials in the NMA (TRANSCEND, ORIENT, and ADVANCE), the treatment group includes patients who discontinued RAASi (10% to 30%) or who may not be on the maximum dose of medication (approximately 60% reported in ORIENT); all of these trials used an intention-to-treat analysis. As such, the reported beneficial OR reported in the NMA applies to a "group" of patients intended to be treated with RAASi that included a distribution of RAASi use, including those on sub-maximal doses and also those who were not taking any RAASi.

  - CADTH undertook several sensitivity analyses to examine the effect of the baseline risks and ORs obtained from the NMA on the cost-effectiveness of patiromer (see Appendix 4), including the assumption that RAASi use at any dose would result in the full benefits observed in the NMA. Another sensitivity analysis was also performed to explore the increased price of patiromer when the maximum dose was prescribed.

- **Drug dose and cost**. The model was based on outcomes observed in the OPAL-HK study. While the mean daily dose of patiromer in OPAL-HK was 21 g, the model assumed 8.4 g per day (with no justification for why this dose was chosen). It is not reasonable to assume similar effectiveness of 8.4 g and 21 g per day.
  - CADTH assumed an average dose of 21 g per day, achieved by requiring half the patients to receive 2 sachets, a conservative approach to achieving mean dose. This increased the cost of patiromer from $9.80 to $14.70 daily. Another sensitivity analysis assuming 75% patients on the maximum dose was listed in Appendix 4.
- **Assumed discontinuation of patiromer.** Discontinuation was estimated from an exponential curve based on OPAL-HK data of 8 weeks' duration. While 82% of patients were observed to remain on patiromer at 8 weeks, after extrapolation, 70% of patients were assumed to discontinue patiromer by 1 year, and all patients discontinued by year 4.5 in the model. According to the CADTH clinical expert, in those patients who initially tolerated patiromer after 8 weeks, it is very likely to be used long-term, if approved.
  - CADTH undertook a sensitivity analysis that assumed long-term use of patiromer (assumed 82% patients on patiromer for the model duration).
- **The reimbursement request is narrower than the Health Canada indication.** The Health Canada indication is for the treatment of hyperkalemia in adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2), while the economic model focused only on CKD stage 3 and 4 patients on RAASi. However, if available, it is likely that patiromer will be used for patients with hyperkalemia that is expected to be persistent (versus due to episodic events), including patients with less and more severe CKD (including off-label indications not approved by Health Canada). Further, it is likely to be used in patients with hyperkalemia, regardless of intent to use RAASi. The cost-effectiveness of use in this larger patient population is

unknown. As there will be no benefits related to RAASi use in this population, it is likely that cost-effectiveness in this larger patient population is less attractive than among those considered by the sponsor in its submitted economic evaluation.

- CADTH was unable to address this limitation.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Base-Case Results

CADTH undertook a stepped analysis, incorporating each change proposed in Table 5 to the sponsor's base case to highlight the impact of each change in Table 6.

The CADTH base case showed that relative to current practice, patiromer was more expensive by $3,871 and more effective by 0.00815 QALY, resulting in an ICER of $475,196 per QALY. The cost savings reported in the sponsor's model were largely due to the assumption of reduction in acute hospitalization in the 6-month period after hyperkalemia (as defined earlier). Further, the increased cost of patiromer in the CADTH base case was due to a

Table 4: Key Assumptions of the Submitted Economic Evaluation Not Noted as Limitations to the Submission

Sponsor's key assumption	CADTH comment
Current practice as comparator for reference case.	Appropriate. According to the clinical expert, other potassium binders are rarely used in clinical practice. However, there is no discussion of the role of diet, which is a mainstay of treatment.
Treatment with patiromer is initialized at serum potassium levels of ≥ 5.5 mmol/L.	Appropriate, as in OPAL-HK and per clinical expert.
RAASi dosing varies with serum potassium levels.	While the association is obtained from observational data, the precise change of RAASi dosing after treatment with patiromer for hyperkalemia is uncertain.
The CPRD database could be generalized to Canada.	Uncertain, but not an unreasonable assumption.
Patiromer discontinuation informed by OPAL-HK.	While initially observed discontinuation is appropriate (due to AEs, and so forth), the continued rate of discontinuation is such that 70% discontinuation at 1 year may not be appropriate. Hyperkalemia may plausibly be even more common over time, particularly in patients in whom kidney function worsens.
The treatment effect from OPAL-HK could be applied beyond 8 weeks.	Uncertain. The patient input notes dietary restriction as management; it is possible that patients may liberalize their diet and the impact on potassium may lessen.
Transition probabilities were unaffected by the occurrence of CV events.	Appropriate.
Patients who experience hyperkalemia would not incur a disutility.	Appropriate for no disutility for hyperkalemia event.
AEs were considered only in the first and second cycles and would cause a patient to discontinue patiromer. AEs were treated only with medications and did not require hospitalization or additional physician consultations.	Appropriate.

AE = adverse event; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; RAASi = renin-angiotensin-aldosterone system inhibitor; SAE = serious adverse event.

substantial proportion requiring 25.2 g per day (average daily dose in OPAL-HK was 21 g). It is notable that even in the sponsor's base case, the QALY gains are estimated to be small, accounting for 0.01749 incremental QALYs (or 6.4 additional days in perfect health); having a small denominator may lead to large changes in the ICER, with changes to the numerator in sensitivity analysis. With no discontinuation after 8 weeks, the ICER was more than $4 million per QALY, as the estimated benefits are small but ongoing drug costs of patiromer were incurred.

Scenario Analysis Results

In the above sensitivity analysis where long-term use is assumed, due to model limitations, no recurrent CV events were allowed, and, as such, this may have underestimated benefit, leading to an over-estimated ICER. However, this may represent the scenario where dietary restrictions of potassium relax over time and, subsequently, use and benefit of RAASi decline but patiromer is continued.

CADTH conducted additional sensitivity analyses on the CADTH base case when the NMA inputs were varied (Appendix 4). Varying the NMA OR inputs by 20% caused the CADTH base case to range from $287,671 to more than $1 million per QALY. Varying baseline event rates

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	None	None
Changes to derive the CADTH base case		
1. Occurrence and cost of acute hospitalization in the 6-month period following development of hyperkalemia (either to 5.5 mmol/L to 6 mmol/L or > 6.0 mmol/L).	The cost of a standard hospital stay was applied ($6,268.75).	In light of the absence of high-quality evidence of causality and modification of acute hospitalization by treatment with patiromer, hospitalization cost was set to $0.
2. Risk of CV event, CV death, and CKD progression are modified by dose of RAASi (full dose from NMA, reduced RAASi dose 50% of benefit reported in the NMA)	The risks at reduced RAASi dose were assumed to be half of the benefit reported in the NMA.	Same event risks for patients on full dose were assumed for patients on reduced dose; the benefits associated with RAASi from the NMA were applied to all patients on an RAASi, regardless of dose.
3. Dose of patiromer	Dose assumed to be either 8.4 g of 16.8 g per day; no patients on maximum dose (25.2 g).	Assumed 50% of patients on the maximum daily dose to align with the dose reported in OPAL-HK (daily average dose 21.2 g); unit cost of patiromer increased from $9.80 to $14.70.
4. Patiromer discontinuation	Discontinuation was estimated from an exponential curve based on OPAL-HK data.	Assumed long-term use of patiromer (no further discontinuation after 8 weeks).
CADTH base case	1 + 2 + 3	

CKD = chronic kidney disease; CV = cardiovascular; NMA = network meta-analysis; RAASi = renin-angiotensin-aldosterone system inhibitor.

[a]Given that bleeding was assumed to be controlled in all patients, no subsequent therapy would be modelled.

[b]Clinical experts consulted by CADTH indicated that weight-based dosing is performed without wasting vial contents, so that actual dose is ± 10% of calculated. It was assumed there would be no wastage and that, over a large number of patients, actual use will approximate weight-based dosing for both recombinant von Willebrand factor or plasma-induced von Willebrand factor.

changed the ICER from $403,713 to $582,390 per QALY. Baseline RAASi discontinuation rate has the least impact on the ICER, given its minimal impact on the incremental QALY gained.

Price reduction analysis determined that a price reduction for patiromer of approximately 85% would be required to achieve an ICER under $50,000 per QALY. If no treatment discontinuation is assumed after 8 weeks (CADTH base case plus reanalysis 4), then a 99% price reduction would be required.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	Patiromer (plus current practice)	137,172	6.189	Dominant
	Current practice	138,411	6.168	—
CADTH reanalysis 1	Patiromer (plus current practice)	134,320	6.189	101,868/QALY
	Current practice	132,537	6.168	—
CADTH reanalysis 2	Patiromer (plus current practice)	136,442	6.196	Dominant
	Current practice	136,969	6.185	—
CADTH reanalysis 3	Patiromer (plus current practice)	138,541	6.189	7,400/QALY
	Current practice	138,411	6.168	—
CADTH reanalysis 4	Patiromer (plus current practice)	156,024	6.193	808,070/QALY
	Current practice	138,411	6.168	—
CADTH base case	**Patiromer (plus current practice)**	**134,948**	**6.196**	**475,196/QALY**
	Current practice	**131,077**	**6.185**	**—**
CADTH base case plus 4	Patiromer (plus current practice)	166,412	6.196	4,053,286/QALY
	Current practice	131,077	6.185	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 7: CADTH Price Reduction Analyses

	ICERs for patiromer (plus current practice) vs. current practice	
Price reduction	Sponsor base case	CADTH reanalysis
No price reduction	Dominant	475,196
25%	Dominant	349,193
50%	Dominant	223,190
75%	Dominant	97,187
80%	Dominant	71,986
85%	Dominant	**46,786**

ICER = incremental cost-effectiveness ratio; vs. = versus.

Issues for Consideration

- Patiromer is indicated for the treatment of hyperkalemia in adults with CKD, with an eGFR of 15 mL/min/1.73 m^2 or greater. However, the CADTH clinical expert indicated that it might continue to be used for patients with an eGFR of less than 15 mL/min/1.73 m^2 until the eGFR is less than 10 mL/min/1.73 m^2 or when dialysis is required.
- The model considers a population on RAASi, and benefits accrue due to greater use of RAASi. However, patiromer is likely to be used in patients with hyperkalemia who are not receiving RAASi.
- A cornerstone of management of hyperkalemia is by dietary restriction of potassium. As dietary restriction may be onerous and may wane if there is a medication to treat, it is plausible that there may be more patients with hyperkalemia (i.e., no longer adhering to diet if they prefer to manage with a medication). It is also plausible that patients on patiromer may relax dietary restrictions, which could lead to attenuating differences in potassium levels (trial was only 8 weeks), and either no benefit in RAASi use or higher dose of patiromer.
- While patiromer sachets are flat priced, the maximum dose (25.2 g) requires 2 sachets, doubling the daily cost. If more patients are prescribed the maximum dose, drug-acquisition costs will increase.
- According to the clinical expert, patients who discontinue patiromer might have higher serum potassium levels compared with baseline, because of less restrictions on diet.
- The sponsor has committed to flat pricing, but the 25.2 g dose is not yet available in Canada.

Overall Conclusions

The sponsor's base case included several assumptions that were not substantiated by quality evidence and were based on surrogate outcomes measured in OPAL-HK, both of which are likely to favour patiromer. First, the model assumed that acute hospitalizations in the 6 months after hyperkalemia can be attributed to hyperkalemia and can be reduced by treating with patiromer; however, this assumption is not supported by reasonable quality evidence. When this assumption is removed, patiromer is no longer dominant, underscoring the significant impact this assumption has on study results. Second, the average dose of patiromer was 21 g, indicating that a proportion of patients required 2 sachets, increasing daily costs. Third, while it is plausible that management of hyperkalemia with patiromer may allow more patients to be treated with RAASi, there is significant uncertainty on the magnitude of this effect, the duration of effect (due to the plausible relaxation in dietary potassium intake over time), and also uncertainty on how the NMA was used to estimate the benefits of RAASi. In the sensitivity analysis, where the same benefits were assumed for reduced dose, the incremental QALY gained by patiromer reduced by half. Combining these 3 factors in the CADTH base case, the ICER of patiromer plus current practice relative to current practice alone was $475,196 per QALY. An 85% price reduction is required to have an ICER less than $50,000 per QALY if continued treatment discontinuation is assumed; then a 99% reduction is needed. Significant uncertainty exists, however, and a greater price reduction would be required if a larger proportion of patients take the maximum dose of patiromer, or if other parameters from the NMA are varied through a plausible range.

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Appendix 1: Cost Comparison Table

Note that this appendix has been formatted for accessibility but has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Hyperkalemia

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Patiromer sorbitex calcium (Veltassa)	8.4 g 16.8 g	Powder	9.8000[b]	8.4 g to 25.2 g daily	9.80 to 19.60	3,577 to 7,154
Cation-exchange resins						
Sodium polystyrene sulfonate (generic)	454 g	Powder	42.0250	15 g to 60 g daily	1.39 to 5.55	507 to 2,027
Calcium polystyrene sulfonate (Resonium Calcium)	1 g	Powder	0.3865[c]	45 g to 60 g daily	17.39 to 23.19	6,348 to 8,464
Diuretics						
Furosemide (Lasix; generic)	10 mg/mL	Oral solution	0.3229	40 mg[d]	1.29	471
	10 mg/mL	Injectable solution	0.8650	40 mg[d]	3.46	1,263
	20 mg 40 mg 80 mg	Tablet	0.0218 0.0327 0.0703[e]	40 mg[d]	0.03	12
Bumetanide (Burinex)	1 mg 5 mg	Tablet	0.7907[c] 3.0184[c]	0.5 mg to 2 mg daily	0.79 to 1.58	289 to 577
Ethacrynic acid (Edecrin)	25 mg	Tablet	0.9556[c]	50 mg to 200 mg daily	1.91 to 7.64	698 to 2,790
Hydrochlorothiazide	12.5 mg 25 mg 50 mg	Tablet	0.0322 0.0157 0.0217	50 mg to 200 mg daily	0.02 to 0.09	8 to 32

Note: All prices are from the Ontario Drug Benefit Formulary (accessed December 2020),[16] unless otherwise indicated, and do not include dispensing fees. Annual prices are based on 365 days per year.

[a]Recommended dosages are from the respective product monographs, unless otherwise indicated.[17-22]

[b]Sponsor's submitted price.[23]

[c]Saskatchewan drug formulary (accessed December 2020).[24]

[d]Dosing based on the National Kidney Foundation: Best Practices in Managing Hyperkalemia in Chronic Kidney Disease.[26]

[e]Alberta drug formulary (accessed December 2020).[25]

Appendix 2: Submission Quality

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Table 9: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing.	No	The model used surrogate end point (serum potassium) to predict use of RAASi and subsequent downstream events (CV events, CV death and CKD progression) based on population data and published literature. The results from a 12-week trial were also extrapolated to a 35-year horizon.
Model has been adequately programmed and has sufficient face validity.	Yes	
Model structure is adequate for decision problem.	No	Recurrent CV events were not allowed in the model, which might underestimate the long-term benefits of patiromer.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	Yes	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	No	Lack of sensitivity analysis on uncertain parameters. For example, evidence for reduction in HK hospitalizations did not meet criteria for either causality or treatment effect with patiromer but was not examined in the sensitivity analysis.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	Yes	

CKD = chronic kidney disease; CV = cardiovascular; HK = hyperkalemia; RAASi = renin-angiotensin-aldosterone system inhibitor.

Appendix 3: Additional Information on the Submitted Economic Evaluation

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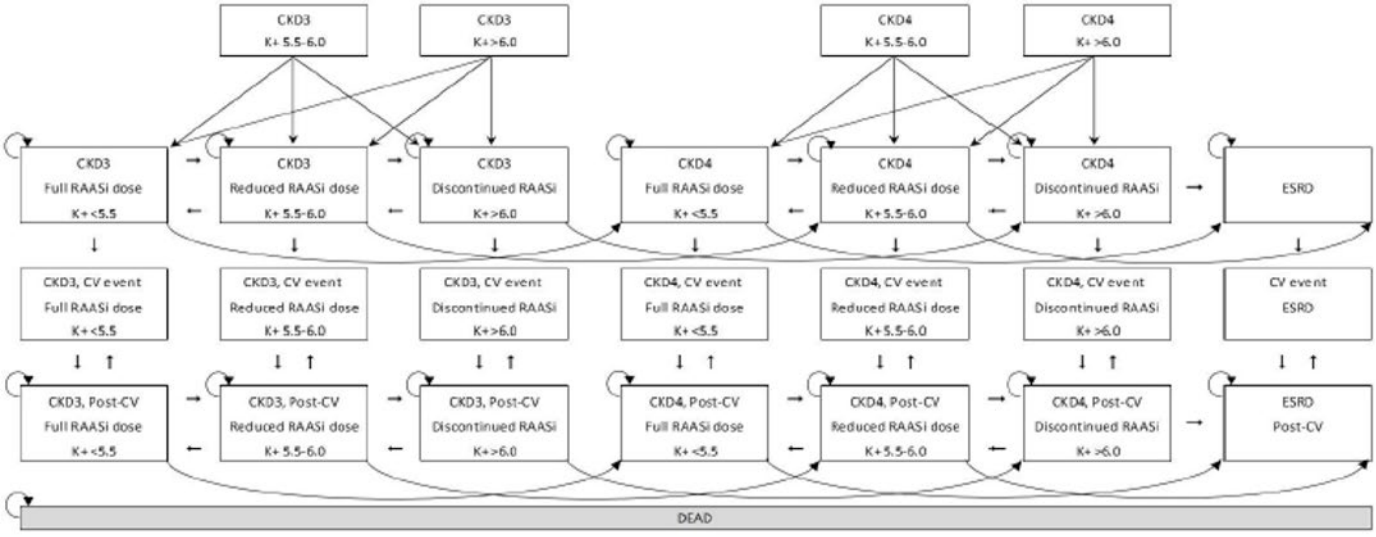
Figure 1: Model Structure



CKD3 = chronic kidney disease stage 3; CKD4 = chronic kidney disease stage 4; CV = cardiovascular; ESRD = end-stage renal disease; K+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: Sponsor's pharmacoeconomic submission.[15]

Detailed Results of the Sponsor's Base Case

Table 10: Discounted Disaggregated Mean Costs for the Probabilistic Sponsor's Reference-Case Analysis

Costs	Patiromer (plus current practice) ($)	Current practice ($)	Incremental ($)
Health state costs			
CKD 3	27,313	27,008	309
CKD 4	55,611	55,499	141
ESRD	47,782	49,298	−1,484
Other costs			
Costs of patiromer	2,793	0	2,793
Cost of RAASi	321	301	19
Cost of concomitant medication	497	496	1
Cost of adverse events	2.76	0	2.76
Total costs	137,172	138,411	−1,239

CKD = chronic kidney disease; ESRD = end-stage renal disease; RAASi = renin-angiotensin-aldosterone system inhibitor.

Source: Table 8.3 in sponsor's pharmacoeconomic submission.[15]

Table 11: Discounted Disaggregated Mean QALYs for the Probabilistic Sponsor's Reference-Case Analysis

Health state	Patiromer (plus current practice) QALYs	Current practice QALYs	Incremental QALYs
CKD 3	1.941	1.916	0.0244
CKD 4	3.710	3.697	0.0113
ESRD	0.5389	0.5555	−0.0170
Adverse event decrements	−0.0011	0.0000	−0.0011
Total QALYs	6.189	6.168	0.0175

CKD = chronic kidney disease; ESRD = end-stage renal disease; QALY = quality-adjusted life-year.

Source: Table 8.3 in sponsor's pharmacoeconomic submission.[15]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

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Table 12: Discounted Disaggregated Mean Costs for the Probabilistic CADTH Reference-Case Analysis

Costs	Patiromer (plus current practice) ($)	Current practice ($)	Incremental ($)
Health state costs			
CKD 3	27,356	27,171	188
CKD 4	55,807	55,846	−9
ESRD	46,801	47,326	−493
Other costs			
Costs of patiromer	4,162	0	4,162
Cost of RAASi	321	303	19
Cost of concomitant medication	498	497	1
Cost of adverse events	2.76	0	2.76
Total costs	134,948	131,077	3,871

CKD = chronic kidney disease; ESRD = end-stage renal disease; RAASi = renin-angiotensin-aldosterone system inhibitor.

Table 13: Discounted Disaggregated Mean QALYs for the Probabilistic CADTH Reference-Case Analysis

Health state	Patiromer (plus current practice)	Current practice	Incremental
CKD 3	1.944	1.929	0.0149
CKD 4	3.723	3.721	−0.00001
ESRD	0.529	0.534	−0.00565
Adverse event decrements	−0.0011	0.0000	−0.0011
Total QALYs	6.196	6.185	0.00815

CKD = chronic kidney disease; ESRD = end-stage renal disease; QALY = quality-adjusted life-year.

CADTH also explored the reason of RAASi discontinuation in a few recent trials from the NMA. All trials adopted an intention-to-treat approach for analysis. The results are summarized in Table 14.

Table 14: RAASi Discontinuation Reported in Recent Trials in the NMA

Study	N	Duration	Reason for discontinuation	Risk of discontinuation (treatment vs. placebo)	Converted annual probability
TRANSCEND (2011)[27]	5,398	4.7 years	All cause	0.21 vs. 0.23	0.049 vs. 0.055
ORIENT (2011)[28]	577	4 years	Hyperkalemia	0.092 vs. 0.053	0.024 vs. 0.014
ADVANCE (2010)[29]	10,640	4.3 years	All cause	0.057 vs. 0.029	0.014 vs. 0.007
HOU (2006)[30]	422	3.4 years	Hyperkalemia	0.073 vs. 0.045	0.022 vs. 0.013

NMA = network meta-analysis; RAASi = renin-angiotensin-aldosterone system inhibitor; vs. = versus.

CADTH undertook additional stepped analyses to explore the risks from Xie et al.'s NMA on the results. The RAASi discontinuation due to hyperkalemia in the model were higher than those from the trials (0.049 to 0.119 versus 0.022 to 0.024), the risk of RAASi discontinuation was thus reduced to a monthly risk of 0.002 in the sensitivity analysis that follows. The baseline risks and relative risks of CV events, CV deaths and CKD progression were also varied by ± 20% to explore the impact on the results.

The parameters varied in the model are summarized in Table 15 and the results of these changes are outlined in Table 16.

Table 15: Sensitivity Analyses on Parameters From the NMA

Parameters	Values in sponsor's base case	Values in CADTH's sensitivity analyses
Baseline risk of CV events	0.0057	0.0045 to 0.0068
Baseline risk of CV death	0.0021	0.0017 to 0.0025
Baseline risk of CKD progression (CKD 3 to CKD 4 or CKD 4 to ESRD)	0.0040	0.0032 to 0.0048
CV events, OR	0.8035	0.6428 to 0.9642
CV death, OR	0.9497	0.7598 to 1.00
CKD progression, OR	0.6370	0.5096 to 0.7644
Risk of transition from reduced RAASi to discontinued RAASi	CKD 3: 0.0042 CKD 4: 0.0105	0.0020

CKD = chronic kidney disease; CV = cardiovascular; NMA = network meta-analysis; OR = odds ratio; RAASi = renin-angiotensin-aldosterone system inhibitor.

Table 16: Sensitivity Analysis Results

Analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
CADTH base case	**Patiromer (plus current practice)**	**134,948**	**6.196**	**475,196/QALY**
	Current practice	**131,077**	**6.185**	**—**
CADTH base case plus baseline event risks plus 20%	Patiromer (plus current practice)	140,983	6.096	403,713/QALY
	Current practice	137,188	6.083	—
CADTH base case plus baseline event risks reduced by 20%	Patiromer (plus current practice)	128,816	6.307	528,390/QALY
	Current practice	124,870	6.297	—

Analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
CADTH base case plus OR event risks increased by 20% (RR = 1 for CV death)	Patiromer (plus current practice)	140,778	6.096	1,061,142/QALY
	Current practice	136,809	6.090	—
CADTH base case plus OR event risks reduced by 20%	Patiromer (plus current practice)	128,779	6.304	287,671/QALY
	Current Practice	125,005	6.288	—
CADTH base case plus RAASi discontinuation risk to 0.002	Patiromer (plus current practice)	134,877	6.196	528,391/QALY
	Current practice	130,926	6.186	—
CADTH base case plus 75% patients on maximum dose	Patiromer (plus current practice)	135,632	6.196	559,198/QALY
	Current practice	131,077	6.185	—

CV = cardiovascular; ICER = incremental cost-effectiveness ratio; OR = odds ratio; QALY = quality-adjusted life-year; RR = relative risk.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 17: CADTH Summary Findings From the Sponsor's BIA

Key takeaways of the budget impact analysis

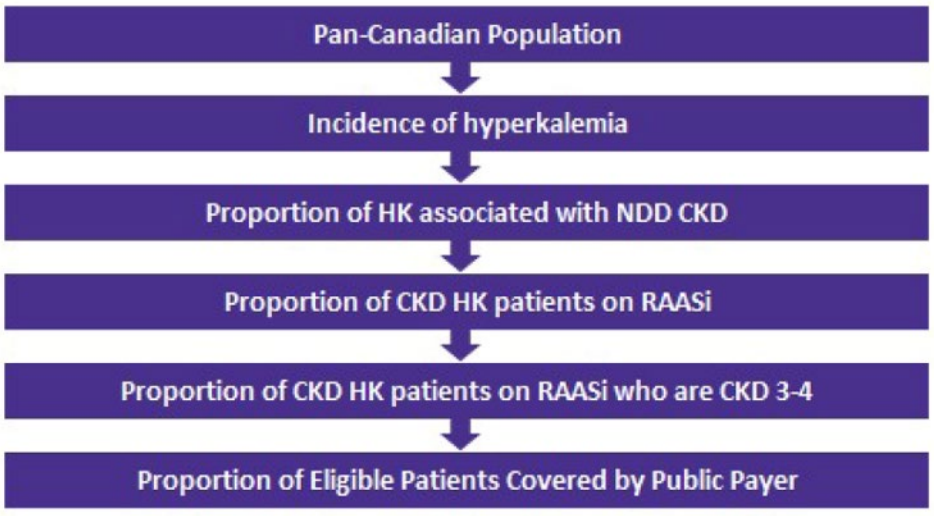
• CADTH identified the following key limitations with the sponsor's analysis:
  ◦ The daily dose of patiromer is underestimated when considering the average daily dose in OPAL-HK.
  ◦ There is uncertainty surrounding the duration of treatment with patiromer, but the sponsor's assumptions are likely underestimated.
  ◦ There is some uncertainty in the market share estimates provided by the sponsor.
• CADTH found the sponsor's estimated budget impact to be significantly underestimated. Based on CADTH reanalyses, the budget impact from the introduction of patiromer is expected to be $24,001,688 in year 1, $36,260,737 in year 2, and $26,685,874 in year 3, for a 3-year total of $86,948,298.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of patiromer sorbitex calcium, hereafter patiromer, for the treatment of adults with CKD stage 3 to 4 on an RAASi with hyperkalemia, defined as serum potassium levels of 5.5 mmol/L or greater. The analysis was undertaken from the perspective of the Canadian public drug plans using an epidemiologic-based approach, with only drug-acquisition costs considered. A 3-year time horizon was used, from 2022 to 2024, with 2021 as a base year. A summary of the sponsor's derivation of the eligible population size is presented in Figure 2.

The relevant comparators for this analysis were the 2 cation-exchange resins sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) which are also used to treat hyperkalemia. In addition, the standard of care (SoC) for hyperkalemia patients includes dietary restrictions and loop diuretics. The reference case scenario included SPS/CPS plus SoC compared with SoC alone. The new drug scenario included patiromer plus SoC, SPS/CPS plus SoC, and SoC alone. Key inputs to the BIA are documented in Table 18.

Figure 2: Sponsor's Estimation of the Size of the Eligible Population



Source: Sponsor's pharmacoeconomic submission.[23]

Table 18: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Target population	
Canadian population in 2021 (adults only, excluding Quebec)	24,794,162
Incidence of hyperkalemia per 1,000 patient-years in adults	4.01[31]
Proportion of HK associated with NDD CKD	46.93%[31]
Proportion of CKD HK patients on RAASi	56.69%[31]
Proportion of CKD HK patients on RAASi who are CKD stage 3 to 4	96.15%[31]
Proportion of eligible patients covered by public payer (pan-Canadian weighted average)	93.64%
Market uptake (3 years)	
Uptake (reference scenario)	
SPS or CPS plus SoC	4.3% / 4.3% / 4.3%
SoC alone	95.7% / 95.7% / 95.7%
Uptake (new drug scenario)	
Patiromer plus SoC	7.5% / 16.9% / 24.1%
SPS or CPS plus SoC	3.46% / 2.43% / 1.64%
SoC alone	89.0% / 80.7% / 74.3%
Cost of treatment (per patient)	
Cost of treatment annually[a]	
Patiromer plus SoC	$1,900.42
SPS or CPS plus SoC	$167.83
SoC alone	$0

CKD = chronic kidney disease; CPS = calcium polystyrene sulfonate; HK = hyperkalemia; NDD = non-dialysis dependent; RAASi = renin-angiotensin-aldosterone system inhibitor; SoC = standard of care; SPS = sodium polystyrene sulfonate.

[a]The annual cost of treatment assumes a treatment duration of 192 days out of the year for patiromer and 61 days for SPS or CPS.

Summary of the Sponsor's BIA Results

The estimated budget impact of funding patiromer for the treatment of adults with CKD stage 3 to stage 4 on an RAASi with hyperkalemia, defined as serum potassium levels of 5.5 mmol/L or greater, was expected to be $3,426,995 in year 1, $7,771,481 in year 2, and $11,205,876 in year 3, with a 3-year total of $22,404,352.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Daily drug cost likely underestimated:** The sponsor assumes in their analysis that the daily dose of patiromer would be either 8.4 or 16.8 g in 99% of patients. However, the mean daily dose of patiromer in OPAL-HK was 21 g. As the 25.2 g dose of patiromer is

not commercialized in Canada, 2 packets of $9.80 each would be required to reach the mean dose from OPAL-HK. The sponsor assumed that this double cost would only be incurred by 1% of patients, which underestimates the drug cost if the daily dose is assumed to be 21 g.

  - As part of the base case to align with the pharmacoeconomic evaluation, CADTH assumed that half (50%) of patients would receive 2 packets of patiromer and would thus incur twice the daily cost.

- **Uncertainty surrounding the length of treatment with patiromer:** The sponsor assumed that the average patient with an incident case of hyperkalemia would be treated with patiromer for 192 days, based on an exponential discontinuation curve applied to the proportion of patients continuing therapy at 8 weeks in OPAL-HK. Clinical experts consulted by CADTH asserted that this was a challenging assumption to accept. They noted that, in eligible patients, patiromer would likely be used until death, dialysis, or a CV event and that, compared with other cation-exchange resins, it is likely that patiromer would be used long-term due to its preferred palatability. Thus, a treatment duration of 192 days underestimates the true treatment duration and thus, the drug-acquisition costs of patiromer.
  - As part of the base case, CADTH assumed that 82% of incident patients would be on patiromer for the full treatment duration that remained in the time horizon of the BIA.
- **Uncertainty around market share assumptions:** The sponsor stated in their report that patiromer would take approximately 75% of the SPS/CPS market by year 3, aligned with physician preference for newer potassium binding therapies. This does not appear to be reflected in the market share assumptions.
  - As part of the base case, CADTH decreased the market shares of SPS/CPS and increased the shares of patiromer accordingly, such that 75% of the SPS/CPS market was taken up by patiromer in year 3.
- **Patients not being treated with RAASi therapy may receive patiromer:** The sponsor's reimbursement request for patiromer suggests that patients would be on RAASi therapy to receive this drug; however, the Health Canada indication is for the treatment of hyperkalemia in any adult with CKD, regardless of RAASi use. The narrower reimbursement request was also noted by the drug plan input received for this review. By limiting the population to those on RAASi the sponsor is likely underestimating the population and associated costs.
  - As part of a scenario analysis, CADTH assumed that patients would receive patiromer regardless of RAASi use status (i.e., 100% of patients were assumed to be on RAASi and eligible).
- **Sponsor only included incident cases in their analysis:** The sponsor assumes that only incident patients would be considered for treatment with patiromer. However, clinical experts consulted by CADTH thought that patients currently being managed for hyperkalemia in other ways would be very likely to switch to patiromer, as it may alleviate dietary restrictions or the necessity of RAASi down-titration. The omission of these patients in the analysis means the budget impact is likely underestimated.
  - CADTH was unable to address this limitation in reanalysis as the model structure did not allow for consideration of patients currently being managed for HK.

CADTH Reanalyses of the BIA

CADTH conducted several revisions as part of the base case by increasing the market share, treatment duration, and assumed daily dose of patiromer.

Table 19: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Increased proportion of patients requiring 2 packets of patiromer	1%	50%
2. Increased treatment duration of patiromer	192 days for all incident patients	3 years for 82% of incident patients in year 1 2 years for 82% of incident patients in year 2 1 year for 82% of incident patients in year 3
3. Increased market share of patiromer in year 3	year 1/ year 2 / year 3	year 1/ year 2 / year 3
Patiromer	7.5% / 16.9% / **24.1%**	7.5% / 16.9% / **24.63%**
SPS/CPS	3.46% / 2.43% / **1.64%**	3.46% / 2.43% / **1.07%**
SoC	89.0% / 80.7% / 74.3%	89.0% / 80.7% / 74.3%
CADTH base case		Reanalysis 1 + 2 + 3

CPS = calcium polystyrene sulfonate; SoC = standard of care; SPS = sodium polystyrene sulfonate.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 20 and a more detailed breakdown is presented in Table 21.

Based on the CADTH base case, the expected budget impact of funding patiromer for the treatment of hyperkalemia is expected to be $24,001,688 in year 1, $36,260,737 in year 2, and $26,685,874 in year 3, for a 3-year total of $86,948,298. If it is expected that patiromer would only be used for short-term use (6 months) then the budget impact decreases to $33,380,417 over 3 years.

One scenario analysis was performed assuming patients would be treated regardless of RAASi usage, which increased the budget impact to $153,375,018 over 3 years. If a price reduction of 85% from the pharmacoeconomic model appraisal is applied to the BIA, the budget impact over 3 years is expected to be $12,835,264.

Table 20: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Three-year total ($)
Submitted base case	22,404,352
CADTH reanalysis 1: Increased dose	33,380,417
CADTH reanalysis 2: Increased treatment duration	58,070,573
CADTH reanalysis 3: Increased market share	22,649,282
CADTH base case	**86,948,298**

Table 21: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	171,494	173,744	175,966	178,204	527,914
	New drug	171,494	3,600,739	7,947,447	11,384,080	22,932,266
	Budget impact	**0**	**3,426,955**	**7,771,481**	**11,205,876**	**22,404,352**
CADTH base case	Reference	171,494	173,744	175,966	178,204	527,914
	New drug	171,494	24,175,432	36,436,703	26,864,077	87,476,212
	Budget impact	**0**	**24,001,688**	**36,260,737**	**26,685,874**	**86,948,298**
CADTH scenario analysis 1: 100% RAASi use	Reference	302,512	306,481	310,401	314,348	931,229
	New drug	302,512	42,644,967	64,273,598	47,387,683	154,306,247
	Budget impact	**0**	**42,338,486**	**63,963,197**	**47,073,335**	**153,375,018**
CADTH scenario analysis 2: 85% price reduction	Reference	171,494	173,744	175,966	178,204	527,914
	New drug	171,494	3,745,422	5,550,276	4,067,480	13,363,178
	Budget impact	**0**	**3,571,678**	**5,374,310**	**3,889,276**	**12,835,264**

RAASi = renin-angiotensin-aldosterone system inhibitor.