MULTI-DISCIPLINARY COLLABORATIVE REVIEW

Application Type: Efficacy supplement

Application Number: 205739/S-038

Priority or Standard: Standard

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Division: Division of Cardiology and Nephrology

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Established Name: Patiromer sorbitex calcium (patiromer)

Trade Name: Veltassa

Applicant: Vifor Pharma Inc**.**

Formulation: Powder for oral suspension

Dosing Regimen: Once daily

Proposed Indication: Treatment of hyperkalemia in adults and pediatric patients ages (b) (4) years and older

Population: This efficacy supplement provides data on pediatric patients 6 years and older

Regulatory Action: Approval

Approved Indication/Population: Treatment of hyperkalemia in adults and pediatric patients ages 12 years and older

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1. Executive Summary

1.1 Summary of Regulatory Action

Veltassa (patiromer sorbitex calcium, patiromer) is a cation exchange polymer that is a potassium binder approved as a powder for oral suspension for the treatment of hyperkalemia in adults. On December 2, 2022, Vifor Pharma Inc**.** submitted an efficacy supplement to NDA 205739 to support use in pediatric patients (b) (4) years of age and older. This submission is intended to address a Pediatric Research and Equity Act (PREA) post-marketing requirement (PMR), described as PMR 2980-1: "A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Veltassa (Patiromer Sorbitex Calcium) for Oral Suspension in Children and Adolescents 2 to 18 Years of Age with Hyperkalemia."

In support of dosing in pediatric patients (b) (4) years of age and older, the Applicant submitted the results of an open-label, baseline-controlled, single arm, multicenter study conducted in pediatric patients 6 to <18 years of age with hyperkalemia and chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (Study RLY5016-206p [EMERALD]). Given its mechanism of action, Veltassa is expected to be effective in treating hyperkalemia in pediatric patients. As such the pediatric development program was designed to obtain dosing, safety, and tolerability data in pediatric patients.

The review team agrees that the submitted data support the safety and efficacy of the proposed dosing regimen in patients 12 years of age and older with hyperkalemia. Although EMERALD included patients 6 to less than 12 years of age, the dosing regimen that was evaluated in these patients did not appear to be effective in reducing serum potassium levels in this age group. Because the available data are not sufficient to determine a safe and effective dosing regimen in patients 6 to less than 12 years of age, labeling recommendations will not be provided for this age group and the indication will be limited to patients 12 years of age and older.

PREA PMR

The Agency considers PMR 2980-1 not fulfilled because of insufficient data in patients 6 to less than 12 years of age and no data in patients 2 to less than 6 years of age. Information to support dosing in pediatric patients less than 12 years will be obtained in an open-label, baseline-controlled, single arm, multicenter study in patients under 12 years of age with hyperkalemia (RLY5016-208p [EMERALD 2]).

(b) (4)

1.2 Benefit-Risk Assessment

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Hyperkalemia is defined as a serum potassium level above the upper limit of normal for age, usually >5 mEq/L in adults and children older than 1 year of age. Persistent or chronic hyperkalemia typically occurs in patients with acute or chronic kidney disease, particularly in those who are on renin-angiotensin-aldosterone system inhibitors (RAASi) or other products that limit the urinary excretion of potassium. Marked elevations in serum potassium levels, generally ≥7 mEq/L, can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis.	Patients with impaired urinary excretion of potassium are at risk of developing hyperkalemia. Marked elevations in serum potassium can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis.
Current Treatment Options	The treatment of hyperkalemia is based on the severity of hyperkalemia. For patients with severe hyperkalemia, treatment focuses on immediate stabilization of the myocardial cell membrane, rapid shifting of potassium into the intracellular space, and total body potassium elimination. For patients with moderate elevations in potassium levels and no electrocardiographic (ECG) abnormalities, restricting dietary potassium, a cation-exchange resin, and/or diuretic can be used to increase excretion. Hemodialysis is also used in patients with kidney failure or when pharmacologic therapy is not sufficient. One cation-exchange resin, sodium polystyrene sulfonate (SPS, Kayexalate), approved for the treatment of hyperkalemia in 1958, includes dosing information for pediatric patients, though the prescribing information also states that studies of safety and efficacy have not been conducted in pediatric patients.	There is an unmet medical need for additional treatments to manage hyperkalemia in pediatric patients.
Benefit	In support of the proposed indication, the Applicant submitted the results of an open-label, baseline-controlled, single arm, multicenter study conducted in pediatric patients 6 to <18 years of age with hyperkalemia and CKD. The mean change in	Given its mechanism of action, patiromer, if administered at an appropriate dose, is expected to be effective in lowering serum potassium levels. At the doses studied, patiromer lowered serum potassium in patients 12 to <18

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	serum potassium from baseline to Day 14 for patients 12 to 17 years of age was -0.5 mEq/L (95% CI -0.8, -0.2) and 50% of these patients had a serum potassium within the normal range at Day 14. The mean change in serum potassium from baseline to Day 14 for patients 6 to less than 12 years of age was -0.1 mEq/L (95% CI -0.7, 0.4), and one patient (13%) had a serum potassium within the normal range at Day 14.	years of age with hyperkalemia. Although the study included patients 6 to less than 12 years of age, based on available data, the dosing regimen that was evaluated did not appear to be effective in reducing serum potassium in this age group.
Risk and Management	In EMERALD, the safety profile of patiromer was generally consistent with that observed in adults. The most common adverse reactions were diarrhea (13%), flatulence (9%), nausea (9%), and hypokalemia (9%).	Diarrhea, flatulence, nausea, and hypokalemia were the most common adverse reactions in pediatric patients treated with patiromer. These risks can be adequately managed via labeling.

1.3 Conclusion Regarding Benefit-Risk

EMERALD demonstrates that patiromer decreases serum potassium levels in pediatric patients 12 to less than 18 years of age with hyperkalemia. Use of patiromer for the treatment of hyperkalemia is supported by evidence from an adequate and well-controlled study in adults that supported approval, with additional pharmacodynamic and safety data in pediatric patients aged 12 years and older. Based on the available data from EMERALD, the dosing regimen that was evaluated in patients 6 to less than 12 years of age did not appear to be effective in reducing serum potassium levels in this age group. No new safety signals were identified in pediatric patients. As such, the available data provide reassurance that the risks of patiromer do not outweigh its benefits in pediatric patients 12 to less than 18 years of age with hyperkalemia.

2. Introduction and Regulatory Background

2.1 Background

On October 21, 2015, the Agency approved Veltassa (patiromer) powder for oral suspension for the treatment of hyperkalemia in adults. At the time of approval, the Agency issued two PMRs under PREA for deferred open label, pharmacodynamic, safety, and tolerability studies in patients 2 to 18 years of age (PMR 2980-1) and infants and toddlers <2 years of age (PMR 2980-2) with hyperkalemia, respectively. In the approval letter, the Agency indicated that pediatric extrapolation of efficacy from adults with hyperkalemia was acceptable.

To address PREA PMR 2980-1, the Applicant conducted Study RLY5016-206p (EMERALD), "A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Veltassa (Patiromer Sorbitex Calcium) for Oral Suspension in Children and Adolescents 2 to 18 Years of Age with Hyperkalemia." The Applicant reported challenges with recruitment and contrary to the advice of the Agency, terminated EMERALD after completing enrollment of 14 patients 12 to <18 years of age in Cohort 1, before the minimum of 12 patients 6 to <12 years of age had been enrolled in Cohort 2 (9 patients enrolled), and before any patients 2 to <6 years of age had been enrolled in Cohort 3. The Applicant proposed adding the youngest cohort to planned Study RLY5016-208p (intended to address PMR 2980-2 in patients birth to <2 years of age with hyperkalemia).

On December 2, 2022, the Applicant submitted an efficacy supplement to extend the indication to pediatric patients (b) (4) years of age and older with hyperkalemia based on the results of EMERALD.

Hyperkalemia is typically defined as a serum potassium >5 mEq/L in adults and children older than 1 year of age. The extracellular concentration of potassium is tightly regulated by the movement of potassium into and out of cells and urinary excretion. In general, persistent hyperkalemia occurs in those with impaired urinary potassium excretion; hence, hyperkalemia is relatively rare in the general population, but is typically seen in patients with acute or chronic kidney disease, particularly in those who are on renin-angiotensin-aldosterone system inhibitors (RAASi). Marked elevations in serum potassium levels, generally ≥7 mEq/L, can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis.

One cation-exchange resin, SPS, approved for the treatment of hyperkalemia in 1958, includes dosing information for pediatric patients, though the prescribing information also states that studies of safety and efficacy have not been conducted in pediatric patients.

2.2 Veltassa Product Information

Patiromer is a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion. The calcium ions in patiromer are exchanged for potassium in the lumen of the gastrointestinal tract, which is then eliminated with the feces, thereby lowering serum potassium levels.

Patiromer powder for oral suspension is currently marketed as 8.4-, 16.8-, and 25.2-gram single-use packets. In the current submission, the Applicant proposes to add a 1-gram packet for dosing pediatric patients.

2.3 Regulatory History Related to Submission

A summary of key regulatory milestones, agreements, and advice relevant to this efficacy supplement is provided in Table 2.

Table 2. Key Regulatory Milestones, Agreements, and Advice

Date/Source	Advice From Agency/Regulatory Action
October 21, 2015 Approval letter	• The Agency stated that, given its mechanism of action, patiromer is expected to be effective in treating hyperkalemia in pediatric patients; therefore, extrapolation was acceptable. Two PREA PMRs were issued: ○ 2980-1: A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Veltassa (Patiromer Sorbitex Calcium) for Oral Suspension in Children and Adolescents 2 to 18 Years of Age with Hyperkalemia (final report submission: 09/2021) ○ 2980-2: same as 2980-1 but in Infants and Toddlers Under 2 Years of Age with Hyperkalemia (final report submission: 07/2025)
January 22, 2016	The Agency received the draft protocol for Study RLY5016-206p (EMERALD) meant to address PMR 2980-1
February 18, 2016 Advice letter	The Agency provided feedback that the study should enroll patients with chronic hyperkalemia likely to require long-term treatment with patiromer

Date/Source	Advice From Agency/Regulatory Action
September 27, 2021 Advice letter	On April 16, 2021, the Applicant submitted a proposal to terminate the ongoing EMERALD study before the minimum 12 patients 6 to <12 years of age and any patients 2 to <6 years of age had been enrolled, and proposed to include patients 2 to <6 years of age in a future study (RLY5016-208p [EMERALD 2]) intended to address PMR 2980-2 (i.e., expand the age group of EMERALD 2 to birth to <6 years of age). The Agency indicated that it did not agree with the Applicant's proposal and voiced concern that the data obtained in patients 6 to <12 years of age may not be sufficient to establish a safe and effective dosing regimen. The Agency also advised against removing patients 2 to <6 years of age from the ongoing EMERALD study and including them in the future EMERALD 2 study because doing so would result in additional delays obtaining the data needed to expand the indication to patients 2 to <6 years of age. The Agency recommended that the Applicant submit the interim clinical study report together with justifications for the proposed changes in the eligibility criteria and sample size to the IND. If pharmacodynamic, dosing and safety data were sufficient to expand labeling to patients 6 to <18 years of age, the Applicant should submit a labeling supplement, while continuing to enroll patients 2 to <6 years of age in the study. In their April 16, 2021, submission, the Applicant also requested a common commentary from FDA and the European Medicines Agency (EMA) regarding their proposal to terminate EMERALD and add the youngest cohort of patients 2 to <6 years of age to the planned EMERALD 2 study. The Agency indicated that it would be happy to participate in joint discussions with the EMA, if needed, after agreement was reached on the aforementioned issues.
October 15, 2021 PREA Non-compliance letter	The Agency issued a PREA non-compliance letter for PMR 2980-1
January 5, 2022 Deferral Extension Denied	The Agency denied the Applicant's deferral extension request for both PREA PMRs
January 13, 2022 Pediatric Cluster Call	The Agency discussed the program with EMA, and reached alignment that the program should be expeditiously completed.
January 19, 2022 Advice letter	In their November 26, 2021, submission, the Applicant proposed to (b) (4) [redacted] The Agency stated that it did not agree with the Applicant's request for the reasons outlined in the September 27, 2021, Advice letter.

Date/Source	Advice From Agency/Regulatory Action
May 13, 2022 Type B meeting	The Applicant submitted a meeting request to discuss a path forward to fulfill their required pediatric assessments. (b) (6) [redacted] The Division and DPMH also requested that the Applicant keep EMERALD open to enrollment for patients 6 to <12 years of age because additional data may be needed to support dosing of patiromer in that age group. The Applicant indicated that they planned to proceed with closing the EMERALD study and committed to obtaining the necessary data to fulfill PMR 2980-1 (b) (4) [redacted]
September 20, 2022 Pre-NDA WRO	The Agency agreed that the proposed content and format of the sNDA submission was acceptable and with the submission of CMC information to support the 1-g packet strength. The Agency did not agree with the Applicant's proposal to not include (b) (4) [redacted] in the submission and advised the Applicant to do so.

Source: Table generated by clinical reviewer and regulatory project manager from review of Agency communications with the Applicant.

3. Patient Experience Data

The Applicant collected information about the palatability (taste and overall liking) of patiromer in children ≥6 years of age on Day 1 (Table 3).

Table 3. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: Patiromer palatability assessments (taste and overall liking) were obtained from patients ≥6 years of age at Day 1, using a 5-point visual analogue scale	

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: Publications:	

4. Interdisciplinary Collaborative Review

4.1 Approach to the Review

This was a joint review between the clinical and clinical pharmacology review disciplines. The clinical review focused on Study RLY5016-206p (EMERALD), which provides support for the pharmacodynamic effects of patiromer on reducing serum potassium levels at the studied doses and its safety in pediatric patients 6 to <18 years of age.

4.2 EMERALD Trial Design

4.2.1 Overview of EMERALD

In support of dosing and safety in pediatric patients 6 to <18 years of age, the Applicant provided data from a baseline-controlled, single arm study, EMERALD, titled "A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 2 to <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD)." The study was conducted at 17 sites in seven countries; six sites screened patients but did not enroll patients. Twenty-three patients were enrolled at two sites in the U.S. (2 patients, 9%), four in Ukraine (13 patients, 56%), two in Georgia (4 patients, 17%), two in Poland (2 patients, 9%), one in Germany (2 patients, 9%).

4.2.2 Initial Protocol and Amendments

The original protocol was dated March 14, 2016 and was amended four times: on September 9, 2016 (amendment 1), April 10, 2017 (amendment 2), October 27, 2017 (amendment 3), and May 20, 2019 (amendment 4). The following were the key changes in each amendment:

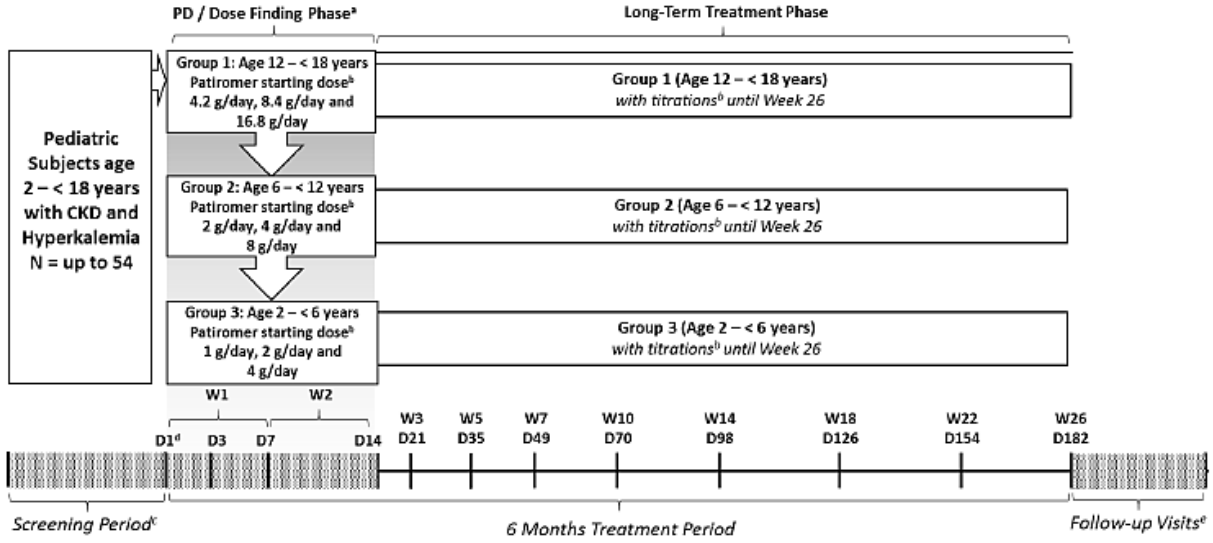
- Amendment 1: (1) allowed for rescreening of serum potassium in patients who were otherwise eligible, (2) added 2-g packets for dosing patient 6 to <12 years of age, and (3) changed the starting dose of patiromer for patients 12 to <18 years of age from 8.4 to 8 g/day, and for patients 6 to <12 years of age from 4.2 to 4 g/day.
- Amendment 2: (1) removed the exclusion of patients taking trimethoprim and cotrimoxazole and removed these medications from the prohibited medications list and indicated that the dose must be stable for 14 days before screening and remain stable during the 14-day PD/Dose Finding Phase, and (2) added that the peritoneal dialysis prescription should not be modified during the 14-Day PD/Dose Finding Phase.

- Amendment 3: (1) made the Day 3 visit optional for patients with a screening serum potassium <5.5 mEq/L (mandatory for patients with a serum potassium ≥5.5 mEq/L), (2) allowed patiromer to be taken with/without food based on the efficacy and safety findings from a food effect study, and (3) indicated that patients on fludrocortisone could be enrolled, that the dose should be stable for at least 28 days before screening, and remain stable during the 14-Day PD/Dose Finding Phase.
- Amendment 4: (1) increased the eGFR eligibility from <60 to <90 mL/min/1.73 m^2, (2) removed the inclusion of patients on peritoneal dialysis (added as exclusion criterion), (3) allowed enrollment of patients who were planning to initiate hemodialysis during the study unless the need for dialysis was anticipated to occur within 6 to 8 weeks of Day 1, and (4) clarified that safety ECG assessments were required for local serum potassium >6 mEq/L.

4.2.3 EMERALD Study Design

EMERALD was an open-label, single arm, study in 23 patients 2 to <18 years of age with hyperkalemia CKD. The study included a 14-day initial pharmacodynamic/dose-finding phase followed by a long-term treatment phase of up to 24-week duration, and a 2-week follow-up period without study drug treatment (Figure 1). Patients were sequentially enrolled according to their age group, starting with Cohort 1 (12 to <18 years of age), Cohort 2 (6 to <12 years of age), and Cohort 3 (2 to <6 years of age).

Figure 1. EMERALD Study Design



D = day; PD = pharmacodynamic; S = screening; W = week.

[a] Dosing of patiromer will first be initiated in the oldest age cohort 12 – < 18 years of age followed by 6 – < 12 years of age and subsequently 2 – < 6 years of age. The first starting dose tested in each age cohort will be the lowest starting dose.

[b] Dose titration for subjects within a dose group will occur using a protocol specified algorithm (see Section 5.2.1) that is based upon starting dose and targeted to achieve and maintain potassium in the target range (3.8 – 5.0 mEq/L).

[c] Subject's eligibility will be assessed during a Screening Period with up to 2 visits (Screening Visit 1, Screening Visit 2). See Section 3.2.1 for details.

[d] For subjects who meet all other eligibility criteria, Screening Visit 1 or Screening Visit 2 may be converted to the Day 1 Visit (Baseline). See Section 3.2.1 for details.

[e] Follow-up will be 1 and 2 weeks after the last dose of patiromer. Follow-up 1 will be an onsite visit where potassium levels will be measured locally and by central laboratory. Follow-up 2 will be via a phone call unless the investigator requests the subject to return for an onsite visit based on potassium level measured in Follow-up 1.

Source: Applicant's Protocol RLY5016-206p

4.2.4 Key Inclusion Criteria

The study included pediatric patients 2 to <18 years of age with an eGFR <90 mL/min/1.73 m^2, including kidney transplant recipients. Patients were required to have two blood or serum potassium measurements of 5.1 to <6.5 mEq/L performed on separate days: (1) a local serum potassium within 2 to 42 days before screening plus at screening, or (2) at the first screening visit plus 2 to 7 days later. Patients were required to be on stable RAASi, beta blockers, fludrocortisone, or diuretics for 28 days and digitalis glycosides, tacrolimus, mycophenolate mofetil or cyclosporine for 14 days before screening. No changes to these medications were allowed during the first 14 days, changes were allowed during the long-term treatment phase.

4.2.5 Key Exclusion Criteria

The study excluded patients with pseudohyperkalemia due to hemolysis or to platelets >500,000/mm^3, leukocytes >70,000/mm^3, or hematocrit >55% at screening, patients on maintenance hemodialysis or peritoneal dialysis (protocol amendment 4 dated May 20, 2019, added the exclusion of patients on peritoneal dialysis), those with renal artery stenosis, current or history of acute kidney injury in the past 3 months (defined by the 2012 Kidney Disease Improving Global Outcomes guidelines).

4.2.6 Dosing and Rationale

Patiromer dosing was based on the median weights for boys and girls within each of the three age categories (12 to <18, 6 to <12, and 2 to <6 years of age) using standard growth data (CDC, 2010). The planned lowest, mid, and highest starting doses in these pediatric cohorts were based on adult doses corresponding to a dose level below the adult efficacy range (4.2 g/day), the starting dose in adults (8.4 g/day), and a higher commonly used dose in adults (16.8 g/day), respectively (Table 4). The Applicant selected the lowest starting doses of 4.2 g/day and 2 g/day, in Cohorts 1 and 2 respectively, as a preemptive safety measure since pediatric patients could be more vulnerable to the risks of patiromer. The study commenced with the lowest dose in the oldest age cohort (12 to <18 years of age).

Table 4. Planned Patiromer Starting Dose Levels for Each Age Cohort

Age Cohort (years)	Starting Dose Levels (g/day)		
	Lowest	Mid	Highest
12 – < 18	4.2	8.4	16.8
6 – < 12	2	4	8
2 – < 6	1	2	4

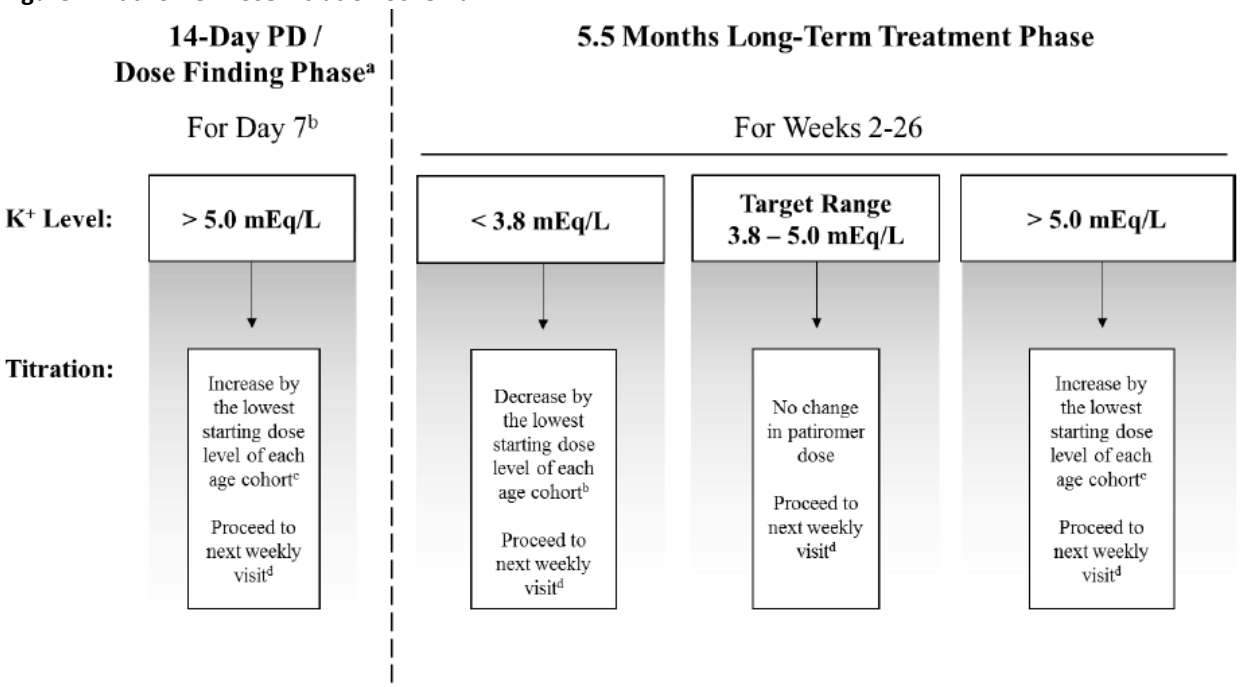
Source: Table 1 of Appendix 16.1.1 for CSR RLY5016-206p. Note: No patients were enrolled in the 2 to <6-year cohort.

4.2.7 Dose Titration and Stopping Criteria

Dose Titration

Patiromer dose titrations (up or down) were allowed to achieve and maintain serum potassium in the target range of 3.8 to 5 mEq/L. The titration dose for increment or decrement was the lowest starting dose for each age group, i.e., 4.2 g/day and 2 g/day in Cohorts 1 and 2, respectively. The criteria for dose titrations are shown in Figure 2.

Figure 2. Patiromer Dose Titration Schema



[a] At Day 3, as a safety measure to ensure that subject exposure to hyperkalemia was not prolonged, patiromer dose could be up-titrated only if the potassium level was ≥5.5 mEq/l and was greater than the most recent locally obtained screening potassium value. Note: At the discretion of the Investigator, the Day 3 visit was optional for participants whose last screening potassium was <5.5 mEq/l; for participants whose last screening potassium was <5.5 mEq/l, the Day 3 visit was to be mandatory;
[b] Down-titration of patiromer dose by the designated decrement for each age cohort or more was allowed for any potassium values <3.8 mEq/l to a minimum patiromer dose of 0 g/day. If patiromer dose required titration, then initiation of the titrated patiromer dose was to occur at the next planned administration;
[c] Dose titration was not required if the potassium decrease from the previous visit was ≥0.5 mEq/l;
[d] If patiromer dose required titration, then initiation of the titrated patiromer dose was to occur at the next planned administration. Participants were required to return for a mandatory safety visit within 7 days if the next scheduled study visit was >1 week after a dose increase had been initiated. Unscheduled visits were to occur during any phase of the study at the discretion of the Investigator.
Source: Applicant's Protocol RLY5016-206p

During the 14-day PD/dose finding phase, patiromer dose up-titration by the permitted titration increment for each age group was allowed beginning at Day 7 for a serum potassium >5 mEq/L. Patients whose serum potassium decreased ≥0.5 mEq/L from the previous visit did not require a dose titration. Patiromer dose down-titration by the permitted titration decrement for each age group or more was allowed for serum potassium levels <3.8 mEq/L to a minimum patiromer dose of 0 g/day. Patients initiated the new patiromer dose at the next planned administration.

Per the protocol, the maximum dose of patiromer was to be 25.2 g/day during the study. For patients in the 2 to <6 year and 6 to <12 year age groups, the highest anticipated doses were 7 g/day and 14 g/day, respectively. The Drug Safety Monitoring Committee (DSMC) could adjust the starting dose level, titration algorithm, and maximum dose level based on their review of PD and safety data. Per the protocol, the DSMC evaluated the following patient-level parameters to assess the patiromer starting dose level:

- Achievement of a target serum potassium range of 3.8 to 5 mEq/L

- A clinically relevant decrease in serum potassium
- The number of dose up-titrations above the starting dose
- Patient safety information

Individual Patient Stopping Criteria
Dosing for an individual patient was permanently discontinued for the following:

- Serum magnesium <1 mg/dL (<0.41 mmol/L) confirmed by re-test
- Potassium-related ECG changes
- Treatment-related SAE
- Pregnancy
- Adverse Event
- Significant protocol deviation
- Non-compliance or poor compliance with study treatment
- If considered in the patient's best interest
- Transition to dialysis during the study and patiromer no longer needed for hyperkalemia

4.2.8 Concomitant Medications and Dietary Restrictions

Information on all concomitant medications (prescription, over the counter, herbal and naturopathic remedies, etc.) was collected at screening and throughout the study.

The use of magnesium supplementation was allowed in patients with serum magnesium levels near or below the lower limit of normal.

Patiromer was taken 3 hours before or 3 hours after administration of other concomitant medications. At the discretion of the investigator, the following drugs could be administered with patiromer: allopurinol, amlodipine, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, cinacalcet, clopidogrel, digoxin, furosemide, glipizide, lisinopril, lithium, metoprolol, phenytoin, rivaroxaban, spironolactone, trimethoprim, valsartan, verapamil, and warfarin.

For patients taking phosphate binders three times per day, one of the daily phosphate binder doses could be replaced by patiromer for the same meal each day at the discretion of the investigator, and the phosphate binder dosed with the two other meals.

In general, patients could continue regular doses of their usual medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, bronchodilators and theophylline, laxatives, and contraceptives. Doses of these medications were kept as stable as possible during the study.

Medications that the investigator deemed necessary for the treatment of an intercurrent illness or pre-existing conditions were generally allowed. Patients requiring analgesia for mild to moderate pain were encouraged to avoid NSAIDs and COX-2 inhibitors and take acetaminophen as an alternative.

For patients taking medications with a narrow therapeutic index, careful monitoring was advised.

Patients were instructed to continue their usual diet during the study.

4.2.9 Statistical Analysis Plan

The statistical analysis plan provided for descriptive analyses. The sample size was based on feasibility rather than power.

Changes from baseline to Day 14 in serum potassium levels (primary efficacy endpoint) were summarized by starting dose and age group using descriptive statistics including the mean, standard deviation, and 95% confidence intervals. Baseline serum potassium was the last non-missing central laboratory serum potassium level before the first dose of patiromer.

The secondary endpoints of proportion of patients with serum potassium levels 3.8 to 5 mEq/L at Day 14, and by visit at any time through Month 6, were described as a percentage and 95% confidence interval.

For patients that transitioned to maintenance hemodialysis or peritoneal dialysis during the study, their data after the start of dialysis was excluded from summary tables and included in listings only.

The safety population and efficacy population were same in this study and defined as all patients who took at least one dose of patiromer.

4.3 Pharmacodynamic Effects of Patiromer

4.3.1 Patient Disposition

A total of 34 patients were screened. Of those, 11 patients did not meet eligibility criteria. A total of 23 patients were enrolled, including 14 patients in Cohort 1 and 9 in Cohort 2 (Table 5). All patients received at least one dose of patiromer, and all completed the 2-week PD/Dose-finding phase.

Table 5. Disposition of Patients

	Cohort 1 (Ages 12 to <18) Starting Dose 4.2 g/day (N=14) n (%)	Cohort 2 (Ages 6 to <12) Starting Dose 2 g/day (N=9) n (%)	Total n (%)
Subjects screened[1]			34
Number of subjects who screen failed[2]			11
Subjects enrolled	14	9	23
Subjects received at least 1 dose of patiromer	14	9	23
Subjects completed the Day 14 visit (PD/dose finding phase)[3]	14 (100)	9 (100)	23 (100)
Subjects completed the Week 26 visit (LT treatment phase)[3]	12 (85.7)	9 (100)	21 (91.3)
Subjects withdrawing before Week 26 visit[3]	2 (14.3)	0	2 (8.7)
Primary reason for early termination[4]			
Adverse event	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Non-compliance with study drug	0	0	0
Other	0	0	0
Investigator decision	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by Sponsor	0	0	0
Withdrawal by subject	2 (100)	0	2 (100)
Withdrawal by parent/guardian	0	0	0

1 Subjects were counted only once, irrespective of the number of times they were screened.
2 Four subjects failed their first screening and were re-screened. Of these, 2 were successfully enrolled and were not counted as screen failures. The other 2 subjects failed the re-screen.
3 Denominator is the number of subjects who received at least 1 dose of patiromer.
4 Denominator is the number of subjects with early termination.
Notes: LT=Long-term; N=Subjects in a cohort; n=Subjects with observation; PD=Pharmacodynamic.

Source: Table 7, RLY5016-206p Clinical Study Report. All but two patients (b) (6)), both in Cohort 1, completed the long-term treatment phase (91%). Patient (b) (6) received the last dose of patiromer on Day 153 (personal and family choice to withdraw from the study) and Patient (b) (6) on Day 76 (personal choice to discontinue participation after turning 18 years of age).

4.3.2 Baseline Characteristics

Baseline demographic and disease characteristics are shown in Table 6. Patients in Cohort 1 accounted for 61% of the study population. Overall, 61% were male, and 100% were white. Although the study did not include a diversity of races, given the mechanism of action of patiromer, the effect on serum potassium is not expected to be affected by race.

All but 2 patients (91%) were enrolled at sites outside the US, and the majority of those (56%) were enrolled in Ukraine. The most common cause of CKD was congenital anomalies of the kidney and urinary tract (CAKUT), which is a common cause of CKD in pediatric patients in the U.S. No patients were on peritoneal dialysis, and two patients were kidney transplant recipients. Most patients were on RAASi at the time of enrollment, and 26% were on diuretics. Of the patients on diuretics, all but one patient (on a homeopathic diuretic called Lespedeza Capitata Extract) were on loop or thiazide diuretics. Given the similarities in the causes of CKD, concomitant medications that were administered in the trial, and other expected similarities in the standard of care for the treatment of hyperkalemia across regulatory regions (e.g., dietary potassium restriction), the findings are expected to be applicable to pediatric patients in the US.

Table 6. Baseline Demographic and Disease Characteristics, Safety Population

Characteristic	**Cohort 1 N=14**	**Cohort 2 N=9**	**Overall N=23**
Sex, n (%)			
Male	11 (79)	3 (33)	14 (61)
Age, years			
Mean (SD)	15 (2)	8 (2)	12 (4)
Median (min, max)	15 (12, 17)	7 (6, 11)	12 (6, 17)
Race, n (%)			
White	14 (100)	9 (100)	23 (100)
Ethnicity, n (%)			
Hispanic or Latino	1 (7)	0	1 (4)
Not Hispanic or Latino	13 (93)	9 (100)	22 (96)
Region, n (%)			
US	2 (14)	0	2 (9)
Non-US	12 (86)	9 (100)	21 (91)
Serum potassium (mEq/L)			
Mean (SD)	5.5 (0.3)	5.6 (0.4)	5.6 (0.4)
Median (min, max)	5.5 (5.1, 6.2)	5.6 (4.8, 6.1)	5.5 (4.8, 6.2)
Peritoneal dialysis, n (%)	0	0	0
Kidney transplant, n (%)	1 (7)	1 (11)	2 (9)
Etiology of CKD, n (%)			
CAKUT	9 (54)	5 (56)	14 (61)
Glomerular disease	1 (7)	2 (22)	3 (13)
Hypertension	0	1 (11)	1 (4)
Other	4 (29)	3 (33)	7 (30)
eGFR (mL/min/1.73 m^2)			
Mean (SD)	29 (13)	26 (8)	28 (11)
Median (min, max)	27 (9, 56)	26 (12, 37)	27 (9, 56)
<30, n (%)	8 (57)	5 (56)	13 (57)

Characteristic	Cohort 1 N=14	Cohort 2 N=9	Overall N=23
Medications, n (%)			
RAASi	8 (57)	8 (89)	16 (70)
Diuretics	6 (43)	0	6 (26)
Tacrolimus	2 (14)	1 (11)	3 (13)
B-blockers	2 (14)	0	2 (9)
Insulin	1 (7)	0	1 (4)

Source: RLY5016-206p Clinical Study Report
Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; min, minimum; max, maximum; N, number of patients in treatment group; n, number of patients with given characteristic; RAASi, renin angiotensin aldosterone system inhibitors; SD, standard deviation.

4.3.3 Protocol Deviations

The Applicant referred to major protocol deviations as "important" deviations defined as violations of initial informed consent, enrollment in violation of the entry criteria, administration of a prohibited medication to a study subject potentially affecting the primary and secondary efficacy endpoints, not discontinuing patiromer when stopping criteria were met, and continuing patiromer dosing after withdrawal from the study; all others were considered minor.

Eight major protocol deviations occurred in four patients (17%), of which one was in Cohort 1 (Patient (b) (6)) and three in Cohort 2 (Patients (b) (6)). The most common major protocol deviations (four deviations in two patients) were related to laboratory assessments followed by study drug (two deviations in two patients).

Laboratory assessment major protocol deviations included

- Enrollment of a patient ((b) (6)) based on laboratory samples collected as a part of the standard of care rather than the screening visit
- Three protocol deviations in Patient (b) (6) including missed safety assessments (e.g., serum fluoride), local instead of central laboratory assessments for some visits, incorrect processing of a potassium sample, and incorrect labeling of a hematology sample

Study drug related major protocol deviations included

- A higher starting dose (8.4 g/day) of patiromer than required per protocol (4.2 g/day) (Patient (b) (6))
- The required study kits were not dispensed during the Week 7 visit (Patient (b) (6))

Two additional major protocol deviations were related to protocol assessments (Patient (b) (6): laboratory assessments were obtained before the informed consent was signed), and study visits (Patient (b) (6) missed the Day 3 visit that was required to recheck serum potassium in patients with a screening potassium of >5.5 mEq/L; the patient's screening serum potassium was 5.7 mEq/L and repeat on Day 7 was 6.1 mEq/L).

All other protocol deviations were minor. No patients were excluded from pharmacodynamic or safety analyses because of protocol deviations.

4.3.4 Pharmacodynamic Effects of Patiromer

As previously noted, the Agency agreed to extrapolation of efficacy from adult to pediatric patients. As such, the objective of the EMERALD was to evaluate safety and to confirm dosing with descriptive statistics of the pharmacodynamic effect on serum potassium.

The primary pharmacodynamic analysis of this study was change in serum potassium levels from baseline to Day 14. As shown in Table 7, the mean change from baseline in serum potassium was -0.5 mEq/L (95% CI -0.8, -0.2) in Cohort 1 and -0.1 (95% CI -0.7, 0.4) mEq/L in Cohort 2.

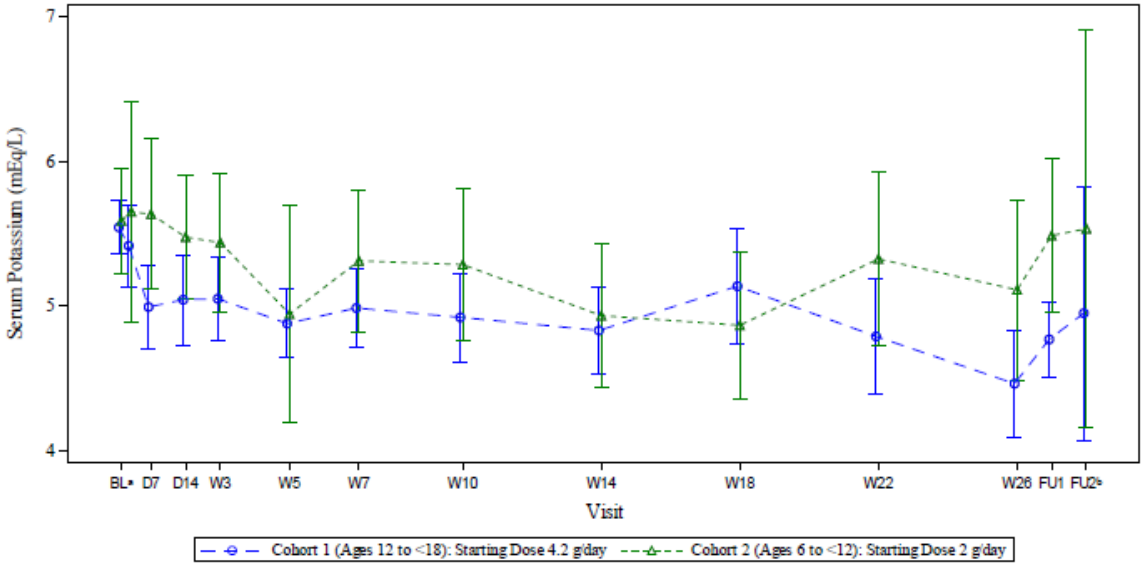
Table 7: Change in Serum Potassium from Baseline to Day 14

	Cohort 1 (N=14)	Cohort 2 (N=9)	Overall (N=23)
Baseline serum potassium (mEq/L)	n=14	n=8	n=22
Mean (SD)	5.5 (0.3)	5.6 (0.4)	5.6 (0.4)
95% CI	(5.4, 5.7)	(5.2, 6.0)	(5.4, 5.7)
Change from baseline to Day 14 (mEq/L)	n=14	n=7	n=21
Mean (SD)	-0.5 (0.5)	-0.1 (0.6)	-0.4 (0.6)
95% CI	-0.8, -0.2	-0.7, 0.4	-0.6, -0.1

Source: Table 17 of CSR RLY5016-206p

Figure 3 displays the mean serum potassium levels over time for the study duration.

Figure 3: Mean (±95% CI) Serum Potassium Levels (Safety Population, N=23)



Source: Figure 14.2.1.1.2 of CSR RLY5016-206p

Dose-Response Relationship

Overview of Data

Patients in Cohort 1 started patiromer treatment at 4.2 g/day (changed in protocol amendment 1 to 4 g/day). At Day 14 (end of the PD/dose finding phase) and the end of the long-term treatment phase, the actual median prescribed dose was 4.2 and 8.4 g/day; the mean (SD) change from baseline in serum potassium was -0.50 (0.5) and -1.1 (0.7) mEq/L, and the proportion of patients with serum potassium in the target range (3.8 to 5 mEq/L) was 50% and 82%, respectively. Patients in Cohort 2 started patiromer treatment at 2 g/day. At Day 14 and at the end of treatment, the actual median prescribed dose was 6 and 8 g/day, the mean (SD) change from baseline in serum potassium was -0.1 (0.6) and -0.5 (1) mEq/L, and the proportion of patients with serum potassium in the target range (3.8 to 5 mEq/L) was 13% and 22%, respectively. Of note, other factors such as concomitant medications that could alter serum potassium levels were not required to be stable during the long-term treatment phase; hence, changes in serum potassium levels after Day 14 could be attributable to factors other than patiromer.

Review Team Conclusion

In Cohort 1 (12 to <18 years of age), the initial 14-day dose finding period seems to be sufficient to achieve potassium control for a large proportion of patients by continuing or only slightly increasing from the starting dose of patiromer. However, in Cohort 2 (6 to <12 years of age), the initial dose (2 g/day) seems insufficient, with the need for multiple up-titrations over several visits, making potassium control less likely to be achieved at the end of the 14-day dose finding period. For Cohorts 1 and 2, the time (median) to serum potassium in the target range (3.8 to 5 mEq/L) was 8 days and 52 days, respectively, while the corresponding median patiromer doses were 4.2 g/day on Day 8 for Cohort 1 and 6 g/day on Day 52 for Cohort 2.

4.3.4.1 Important Patient Subgroups

Prespecified subgroup analyses included age (12 to <18, 6 to <12, and 2 to <6 years of age), sex, and race. The study enrolled 100% white participants, precluding subgroup analyses by race. No patients 2

to <6 years of age were enrolled. Analyses for patients 12 to <18 years of age and 6 to <12 years of age are described in Section 4.3.4.

4.3.5 Acceptability of the Proposed Dosing Recommendations

The proposed dosing regimen of patiromer is acceptable for the treatment of hyperkalemia in pediatric patients 12 to <18 years of age but not for the treatment of hyperkalemia in patients 6 to <12 years of age.

For patients 12 to <18 years of age with hyperkalemia:

- Based on the results of EMERALD (Table 7), the review team agrees with the starting dose of 4 g/day and dose increments of 4 g at 1-week or longer intervals for treating patients 12 to <18 years of age (Cohort 1) with hyperkalemia.

(b) (4)

[redacted]

4.3.5.1 Effect of 4 g/day Patiromer Dose as Compared to 4.2 g/day

The proposed starting dose is 4 g/day in pediatric patients 12 to <18 years of age. In EMERALD, patients in Cohort 1 received a patiromer starting dose of 4.2 g/day (provided as a 4.2 g sachet). The study drug formulation used in clinical studies was identical to the current commercial Veltassa powder for oral suspension product approved for use in adults and differs only in the packet size.

Based on simulations from population PD models, distributions of serum potassium change from baseline in pediatric patients were comparable across all the evaluated starting dose levels (ranging from 4 g/day to 16.8 g/day), suggesting that a starting dose of 4 g/day is likely to yield an effect that is similar to 4.2 g/day (refer to Figure 13). Further, because the patiromer dose will be titrated according to serum potassium levels and tolerability, the difference between 4.2 g and 4 g is not anticipated to be clinically relevant.

4.3.5.2 Similarity Between the To-be-marketed Formulation and the Clinical Trial Formulation

In the EMERALD study, patiromer was provided open label to patients as a powder for oral suspension in packets with appropriate labeling. The individual packets were assembled as a kit for dispensing the adequate amount of patiromer for each patient. Each packet inside an individual kit contained either 4.2 g, 2 g, or 1 g patiromer. Neither the 4.2 g nor 2 g packets are currently proposed in the to-be-marketed strengths.

The planned to-be-marketed pediatric presentation will contain 1 g patiromer per sachet suitable for increments/decrements of 1 g/day and multiples thereof for individualized dose titration based on serum potassium levels. The 1 g packet was proposed to be used only in patients 2 to <6 years of age (Cohort 3) in the EMERALD study. However, because the study was terminated before any patient in that cohort was enrolled, the 1 g packet was not used in clinical studies. Based on the Office of Pharmaceutical Quality assessment, the qualitative and quantitative composition (in weight %), the manufacturing process steps, the product release specification, the qualitative and quantitative composition of primary packaging material, as well as the recommended storage condition are the same for the 1 g packet, 2 g packet, and 4.2 g packet. The batch analysis data of patiromer 1 g, 2 g, and 4.2 g packets are comparable and within specification.

4.4 Safety Results

4.4.1 Important Safety Issues with Patiromer and Related Drugs

As previously noted, SPS, approved for the treatment of hyperkalemia in 1958, includes dosing recommendations for pediatric patients in labeling. The prescribing information for SPS contains warnings for intestinal necrosis, hypokalemia, electrolyte disturbances (e.g., hypomagnesemia and hypocalcemia), and systemic alkalosis. Common adverse reactions of SPS include gastric irritation, anorexia, nausea, vomiting, constipation, hypokalemia, hypocalcemia, hypomagnesemia, and significant sodium retention. Rare adverse reactions include fecal impaction in elderly patients, intestinal necrosis, and intestinal obstruction when used with aluminum hydroxide.

The prescribing information for patiromer contains warnings and precautions for severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, and hypomagnesemia. In the clinical trials conducted to support the approval of patiromer in adults, the most common adverse reactions were constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence. Constipation generally resolved during the course of treatment. Gastrointestinal adverse reactions were the most commonly reported adverse reactions leading to discontinuation of patiromer. Mild to moderate hypersensitivity reactions were also reported.

Additional potential safety concerns based on the mechanism of action of patiromer, include (1) adverse effects of sorbitol (patiromer contains sorbitol as part of the counterion complex) including gastrointestinal symptoms (abdominal pain, diarrhea, and vomiting), hyperglycemia, lactic acidosis, and edema, (2) hypercalcemia (calcium is the exchange ion in this product), and (3) fluoride accumulation (calcium fluoride is a degradation product of patiromer).

4.4.2 Safety Analysis Set and Overall Exposure

Safety analyses focused on the “safety population,” which included 23 enrolled patients who received at least one dose of patiromer. Safety evaluations included vital signs, physical examinations, and laboratory tests, which were performed at regular intervals.

In EMERALD, 23 patients received at least one dose of patiromer including 21 patients exposed for at least 22 weeks (12 in Cohort 1, 9 in Cohort 2).

4.4.3 Categorization of Adverse Events

The Applicant categorized AEs and SAEs by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. An AE was defined as any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study drug, irrespective of its relationship with the study drug. An SAE was defined as an event that resulted in death, was life-threatening, required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was a medically important event. A treatment-emergent adverse event (TEAE) was defined as an AE that occurred or worsened after the first dose of study drug. For AEs with a missing onset date, the AE was considered treatment-emergent unless there was evidence to the contrary. Events occurring from the time of informed consent to the end of the last study visit were collected as AEs.

4.4.4 Overall Adverse Event Summary

Overall, 15 patients (65%) experienced at least one TEAE including 10 patients (71%) in Cohort 1 and 5 patients (56%) in Cohort 2 (Table 8). Most reported AEs were mild or moderate in severity. No SAEs were reported and no TEAEs led to permanent discontinuation of patiromer or withdrawal from the study.

Table 8. Overview of Treatment-Emergent Adverse Events, Safety Population

	Age Group		
	Cohort 1 (Ages 12 to <18) Starting Dose 4.2 g/day (N=14)	**Cohort 2 (Ages 6 to <12) Starting Dose 2 g/day (N=9)**	**All Cohorts (N=23)**
Number of subjects with any TEAEs	10 (71.4)	5 (55.6)	15 (65.2)
Highest severity			
Mild	2 (14.3)	3 (33.3)	5 (21.7)
Moderate	7 (50.0)	2 (22.2)	9 (39.1)
Severe	1 (7.1)	0	1 (4.3)
Study drug-related TEAEs	3 (21.4)	1 (11.1)	4 (17.4)
Study drug-related GI TEAEs[1]	2 (14.3)	0	2 (8.7)
Serious TEAEs	0	0	0
Serious study drug-related TEAEs	0	0	0
Serious GI related TEAEs[1]	0	0	0
TEAEs leading to study drug modification[2]	2 (14.3)	1 (11.1)	3 (13.0)
TEAEs leading to study drug dose increase	0	0	0
TEAEs leading to study drug dose reduction	1 (7.1)	1 (11.1)	2 (8.7)
TEAEs leading to study drug dose interruption	2 (14.3)	0	2 (8.7)
TEAEs leading to study drug discontinuation	0	0	0
TEAEs leading to death	0	0	0

1 GI TEAEs include all TEAEs with a MedDRA (Version 23.1) system organ class of GI Disorders.
2 Study drug modification includes dose reduced, dose increased, and dose interrupted based on the adverse event Case Report Form.
Notes: GI=Gastrointestinal; MedDRA=Medical Dictionary for Regulatory Activities; N=Subjects in a cohort; TEAE=Treatment-emergent adverse event.

Source: RLY5016-206p Clinical Study Report

The most common TEAEs, occurring in two or more patients, were diarrhea, nasopharyngitis, oropharyngeal pain, and renal impairment, each reported in 3 patients (13%); and flatulence, nausea, decreased appetite, hypokalemia, and anemia, each reported in 2 patients (9%). Review of TEAEs by age group did not reveal any obvious patterns; however, sample sizes were limited (Table 9).

Table 9. Treatment-emergent Adverse Events by System Organ Class and Preferred Term, Safety Population

	Actual Treatment for Period 01		
	Cohort 2 (Ages 6 to <12): Starting Dose 2 g/day (N = 9)	Cohort 1 (Ages 12 to <18): Starting Dose 4.2 g/day (N = 14)	Total (N = 23)
Body System or Organ Class/Dictionary-Derived Term	**n (%)**	**n (%)**	**n (% of Total)**
Gastrointestinal disorders	0 (0.0)	6 (42.9)	6 (26.1)
Diarrhoea	0 (0.0)	3 (21.4)	3 (13.0)
Flatulence	0 (0.0)	2 (14.3)	2 (8.7)
Nausea	0 (0.0)	2 (14.3)	2 (8.7)
Abdominal pain	0 (0.0)	1 (7.1)	1 (4.3)
Constipation	0 (0.0)	1 (7.1)	1 (4.3)
Dyspepsia	0 (0.0)	1 (7.1)	1 (4.3)
Frequent bowel movements	0 (0.0)	1 (7.1)	1 (4.3)
Infections and infestations	3 (33.3)	2 (14.3)	5 (21.7)
Nasopharyngitis	2 (22.2)	1 (7.1)	3 (13.0)
Human herpesvirus 6 infection	1 (11.1)	0 (0.0)	1 (4.3)
Infection	0 (0.0)	1 (7.1)	1 (4.3)
Otitis externa	0 (0.0)	1 (7.1)	1 (4.3)
Severe acute respiratory syndrome	1 (11.1)	0 (0.0)	1 (4.3)
Upper respiratory tract infection	0 (0.0)	1 (7.1)	1 (4.3)
Investigations	0 (0.0)	3 (21.4)	3 (13.0)
Blood calcium decreased	0 (0.0)	1 (7.1)	1 (4.3)
Blood calcium increased	0 (0.0)	1 (7.1)	1 (4.3)
Blood creatinine increased	0 (0.0)	1 (7.1)	1 (4.3)
Body temperature increased	0 (0.0)	1 (7.1)	1 (4.3)
Urine output increased	0 (0.0)	1 (7.1)	1 (4.3)
Metabolism and nutrition disorders	1 (11.1)	3 (21.4)	4 (17.4)
Decreased appetite	0 (0.0)	2 (14.3)	2 (8.7)
Hypokalaemia	1 (11.1)	1 (7.1)	2 (8.7)
Metabolic acidosis	0 (0.0)	1 (7.1)	1 (4.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	3 (21.4)	3 (13.0)
Oropharyngeal pain	0 (0.0)	3 (21.4)	3 (13.0)
Epistaxis	0 (0.0)	1 (7.1)	1 (4.3)
Rhinorrhoea	0 (0.0)	1 (7.1)	1 (4.3)
Nervous system disorders	0 (0.0)	2 (14.3)	2 (8.7)
Dizziness	0 (0.0)	1 (7.1)	1 (4.3)
Parosmia	0 (0.0)	1 (7.1)	1 (4.3)
Somnolence	0 (0.0)	1 (7.1)	1 (4.3)
Renal and urinary disorders	0 (0.0)	3 (21.4)	3 (13.0)
Renal impairment	0 (0.0)	3 (21.4)	3 (13.0)
Blood and lymphatic system disorders	1 (11.1)	1 (7.1)	2 (8.7)
Anaemia	1 (11.1)	1 (7.1)	2 (8.7)
Injury, poisoning and procedural complications	0 (0.0)	2 (14.3)	2 (8.7)
Medication error	0 (0.0)	1 (7.1)	1 (4.3)
Skin abrasion	0 (0.0)	1 (7.1)	1 (4.3)
Psychiatric disorders	0 (0.0)	2 (14.3)	2 (8.7)
Dysphoria	0 (0.0)	1 (7.1)	1 (4.3)
Psychomotor retardation	0 (0.0)	1 (7.1)	1 (4.3)
Cardiac disorders	0 (0.0)	1 (7.1)	1 (4.3)
Arrhythmia	0 (0.0)	1 (7.1)	1 (4.3)
General disorders and administration site conditions	0 (0.0)	1 (7.1)	1 (4.3)
Fatigue	0 (0.0)	1 (7.1)	1 (4.3)
All	5 (55.6)	10 (71.4)	15 (65.2)

Source: Reviewer analysis, JMP Clinical

4.4.5 Deaths

There were no deaths in the study.

4.4.6 Non-Fatal Treatment Emergent Serious Adverse Events

There were no reported SAEs in the study.

4.4.7 Dropouts or Discontinuations Due to Adverse Events

No patients permanently discontinued patiromer because of TEAEs. Patiromer dosing was temporarily interrupted in two patients (9%), both in Cohort 1, because of TEAEs of diarrhea in one patient and hypokalemia in the other patient. Narratives for these patients are provided below.

- *Patient* (b) (6): A 12-year-old male with a history of CKD secondary to renal dysplasia, coagulopathy, cytogenetic abnormality, secondary hyperparathyroidism, strabismus, acidosis,

cachexia, hyperkalemia, prematurity, growth retardation, scoliosis, ataxia, intellectual disability, hypertension, café au lait spots, and hyperkeratosis follicularis. Concomitant medications included amlodipine, cholecalciferol, calcium carbonate, metoprolol, multi-vitamins, sodium bicarbonate, bupivacaine, heparin, metamizole, paracetamol, simethicone, piritramide (an analgesic), omeprazole, and enoxaparin. The patient's screening/Day 1 (b) (6)) serum potassium was 6 mEq/L, and patiromer 4.2 g daily was initiated.

On Day 3 (b) (6)), the patient had AEs of mild diarrhea and flatulence. Patiromer was continued and both AEs were resolved on Day 5 (b) (6)). The patiromer dose was increased to 8.4 g daily on Day 7 (b) (6)), to 12.6 g daily on Day 15 (b) (6)), 16.8 g daily on Day 22 (b) (6)) for persistent hyperkalemia (serum potassium 5.3-5.8 mEq/L). On Day 25, (b) (6)), the patient had an AE of nausea (mild) that resolved on Day 28 (b) (6)). Patiromer dosing was not changed. On Day 32 (b) (6)), the patient had an AE of non-serious mild constipation. On Day 35 (b) (6)), local and central laboratory serum potassium was 5 mEq/L and 5.4 mEq/L, respectively, and the patiromer dose was reduced to 12.6 g daily because of the constipation. Two days later, on Day 37 (b) (6)), the constipation was reported as resolved.

On Day 68 (b) (6)), the patient had an AE of non-serious moderate diarrhea and mild upper respiratory tract infection. Patiromer was interrupted because of diarrhea. On Day 75 (b) (6)), the diarrhea and upper respiratory tract infection had resolved and patiromer was restarted at a dose of 12.6 g daily on Day 77 (b) (6)). The patient continued patiromer to study completion without further events of diarrhea.

- *Patient* (b) (6): A 17-year-old male with a history of CKD secondary to vesicoureteric reflux, acidosis, growth retardation, secondary hyperparathyroidism, hyperphosphatemia, hypertension, anemia of CKD, proteinuria, and Perthes disease. Concomitant medications included calcium acetate, darbepoetin alpha, sodium hydrogen carbonate, calcitriol, cholecalciferol, ramipril, somatotropin, furosemide, sevelamer carbonate, midazolam, metamizole, paracetamol, and iron sucrose.

  On Day 1 (b) (6)), the patient's eGFR was 10 mL/min/1.73 m^2 and serum potassium was 5.6 mEq/L. Patiromer 4.2 g daily was initiated. On Day 106 (b) (6)), the patient had an AE of worsening renal function and hemodialysis was initiated. Two days later, on Day 108 (b) (6)), the patient had an AE of mild hypokalemia (serum potassium not provided). Patiromer was continued and the event was reported as resolved on the same day. On Day 125/Week 18 (b) (6)), the patient's local and central laboratory serum potassium was 3.8 mEq/L and 4.3 mEq/L, respectively. One week later, on Day 132 (b) (6)), the patient had mild hypokalemia with local and central laboratory serum potassium of 3.7 mEq/L and 4 mEq/L, respectively. Patiromer dosing was interrupted. It is not clear when patiromer was restarted; the patient continued the same dose of patiromer until the end of the study (last dose on Day 188 (b) (6)).

4.4.8 Adverse Events of Interest

The protocol did not specify AEs of interest. The Applicant evaluated gastrointestinal TEAEs, "renal function events" defined as those that map to the Standardized MedDRA Queries (SMQs) narrow terms Acute Renal Failure or Chronic Kidney Disease, and allergic reactions as TEAEs of special interest. Given

the study population and mechanistic implausibility of patiromer to cause kidney injury, these events are not evaluated further. In addition to gastrointestinal AEs and allergic reactions, hypokalemia, hypomagnesemia, hyperglycemia, lactic acidosis, edema, hypercalcemia, and fluoride accumulation were also evaluated as AEs of interest.

Gastrointestinal Adverse Events
Six patients (26%) reported AEs in the SOC Gastrointestinal Disorders, all were in Cohort 1. These included diarrhea in 3 patients (13%), flatulence in 2 patients (9%), nausea in 2 patients (9%), and abdominal pain, constipation, dyspepsia, and frequent bowel movements in each of one patient (4%). The diarrhea was reported as moderate in all three patients; all other events were mild. One event of diarrhea led to temporary patiromer dose interruption ((b) (6); see Section 4.4.7 for the patient's narrative) and the patiromer dose was reduced because of an AE of constipation in one patient ((b) (6); see Section 4.4.7 for the patient's narrative). All events resolved despite continuation of patiromer, none led to permanent study drug discontinuation. Overall, these events were consistent with the gastrointestinal adverse reactions described in adults.

Hypokalemia
Two patients (9%) had AEs of hypokalemia, one in Cohort 1 and one in Cohort 2. Both events were mild and did not lead to permanent discontinuation of patiromer. The patiromer dose was temporarily interrupted for hypokalemia (3.7 mEq/L) in one patient after the patient initiated hemodialysis ((b) (6); see Section 4.4.7 for the patient's narrative) and reduced in one patient ((b) (6)) from 8 to 6 g/day for a serum potassium of 3.1 mEq/L, with resolution of the hypokalemia. The patient remained normokalemic on patiromer 6 g/day.

Other Adverse Events of Interest
One patient (4%) in Cohort 1 ((b) (6)) had an AE of blood calcium increased on Day 185, one day after the last dose of patiromer. The AE was mild (serum calcium 10.8 mg/dL, patient's baseline 10 mg/dL) and was resolved on follow-up (Day 190 serum calcium was 9.5 mg/dL) .

No TEAEs were reported for hypomagnesemia, hyperglycemia, lactic acidosis, edema/swelling, fluoride abnormalities, or allergic reactions.

Laboratory Assessments, Vital Signs, and ECGs
No clinically meaningful or obvious trends were observed.

No patient had a serum potassium <3 mEq/L. One patient (4%) in Cohort 2 had a serum potassium of 3 to <3.5 mEq/L at Week 26 (resolved on follow-up). There were no potassium-related ECG abnormalities.

There were no significant changes in serum magnesium and no patient had a serum magnesium <1.4 mg/dL at any timepoint in the study (normal range 1.5 to 2.5 mg/dL for 1 to 17 years of age).

There were no trends in serum calcium towards hypercalcemia. At baseline, the mean (SD) serum calcium was 9.4 (0.8) mg/dL in Cohort 1 and 9.4 (0.7) mg/dL in Cohort 2. On Day 14, the mean (SD) change from baseline was -0.2 (0.4) mg/dL in Cohort 1 and 0 (0.5) mg/dL in Cohort 2. At Week 26, mean (SD) calcium change from baseline was -0.9 (0.9) mg/dL in Cohort 1 and -0.2 (1.6) mg/dL in Cohort 2.

There was no evidence of elevated serum fluoride levels from baseline (normal levels are usually <100 ng/mL). At baseline, the mean (SD) serum fluoride values were 29.8 (17.5) ng/mL in Cohort 1 and 47.4 (39.7) ng/mL in Cohort 2. On Day 14, mean (SD) fluoride change from baseline was -0.9 (9.4) ng/mL in Cohort 1 and 19.5 (44.5) ng/mL in Cohort 2. At Week 26, mean (SD) fluoride change from baseline was 9.5 (13.1) ng/mL in Cohort 1 and 1.9 (15.1) ng/mL in Cohort 2.

4.4.9 Safety Summary and Conclusion

The safety findings in EMERALD are consistent with the findings described in the current patiromer label. No new safety signals were noted in EMERALD.

5. Labeling Recommendations

Major changes to the finalized prescribing information (PI) as compared to the Applicant's draft PI are summarized below.

- The age range for the proposed indication was revised to use in patients 12 years of age and older (b) (4) Similarly, the Pediatric subsection in the Clinical Studies section was revised to focus on the indicated population (i.e., patients 12 to 17 years of age).
- Labeling was revised to include information on the recommended time interval between dose-titration steps in pediatric patients.
- The Pediatric Use section was updated to include the basis for approval in pediatric patients 12 years of age and older, a statement indicating that safety and efficacy have not been established in pediatric patients below the age of 12 years, and information on the relevant pharmacodynamic effects of patiromer on serum potassium levels in the (b) (4) pediatric population 6 to <12 years of age.
- Additional editorial revisions were made throughout the PI. The Drug Interactions section was revised to improve clarity and concision.

6. Appendix

6.1 Pharmacometrics Review

6.1.1 Executive Summary

The Applicant is seeking approval to extend the indication for Veltassa (patiromer) to pediatric patients aged (b) (4) years and older with hyperkalemia. Veltassa is a non-absorbed cation exchange polymer that contains a calcium-sorbitol counterion through binding of potassium in the lumen of the gastrointestinal tract to reduce the concentration of free potassium in the gastrointestinal lumen to reduce serum potassium level. The key pharmacometrics findings are summarized below.

- In Cohort 2 (age: 6 to <12 years), the primary efficacy endpoint, the change in serum potassium from baseline to day 14, was NOT achieved.[1] Therefore, the starting dose for pediatric patients 6 to <12 years of age was not assessed.
- In Cohort 1, model-predicted pediatric (age: 12 to <18 years) change in serum potassium from baseline to day 14 stratified by dose groups showed that a 4 g/day patiromer starting dose yields a comparable efficacy as 4.2 g/day patiromer starting dose. Therefore, the Applicant's recommended starting dose of 4 g/day for pediatrics (age: 12 to <18 years), which can be titrated based on monitored serum potassium level[2], is acceptable.

6.1.2 Population PD analysis

6.1.2.1 Review Summary

The applicant's population pharmacodynamic (PopPD) analysis of Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion through binding of potassium in the lumen of the gastrointestinal tract to reduce the concentration of free potassium in the gastrointestinal lumen to reduce serum potassium level, is acceptable to support the current submission as outlined in Table 10. The applicant's final PopPD model adequately described the serum potassium concentrations with time after patiromer administration. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted serum potassium concentrations without any obvious bias over time or predicted concentrations. The prediction-corrected visual predictive check plots showed a good agreement between the observed and the simulated serum potassium concentrations. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 10: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Myocardial infarction (yes versus no), type 2 diabetes (yes versus no), age and eGFR were identified as statistically significant covariates.	The applicant recommendation that starting dose 4 g/day for pediatric patients 12 to 17 years of age is acceptable.
	Extrinsic factor	NA	NA

[1] Labeling, page 12 (link)
[2] Labelling page 2 (link)

Utility of the final model		**Reviewer's Comments**
Derive exposure metrics for Exposure-response analyses		

Source: Reviewer table

6.1.2.2 Introduction

The primary objectives of applicant's analysis were to:

- A PD dose-response model was developed to simultaneously characterize patiromer effects on serum potassium levels in adults and pediatric patients (age: 6 to <18).
- Confirm the patiromer starting dose required for pediatric patients to yield serum potassium responses comparable to those observed in adults at the established efficacious dose of 8.4 g/day.

6.1.2.3 Population PD Model development

Data

The pooled analysis population consisted of both pediatric and adult patients from one pediatric phase 2 study (RLY5016-206p), one adult phase 2 study (RLY5016-205), and one adult phase 3 study (RLY5016-301), shown in Table 11. Study RLY5016-206p included 14 pediatric patients aged 12 to <18 years and 9 patients aged 6 to <12 years with CKD. Studies RLY5016-301 and RLY5016-205 consisted entirely of adult patients with CKD. There were 23 pediatric and 548 adult patients in total in the analysis population and the pediatric population contributed 337 observations shown in Table 12. The dose summary for participants receiving at least one dose of patiromer stratified by studies was shown in Table 13 with baseline demographic covariates for analysis shown in Table 14.

Data Imputation

There is no missing dataset in the study. Therefore, there is no data imputation.

Table 11: Summary of Clinical Study Designs

Study summary	Treatment	Planned study duration	Population	Treated patients	PD Samples*
RLY5016-206p					
Open-label, multiple-dose, PD, tolerability	Up to 25.2g (QD)	4-day Dose Finding Period followed by an up to 5.5 month Long-Term Treatment Phase	Pediatric patients (6 to < 18 years of age) with CKD and hyperkalemia	23 children	12 serum potassium levels
RLY5016-205					
Open-label, randomized, parallel arm, dose-ranging, dose titration	Starting doses of 8.4g to 33.6g/day (as divided doses BID)	8 week Treatment Initiation Period followed by a 44 week Long Term Maintenance Period	Hypertensive patients with diabetic neuropathy and receiving RAASi	305 adults[a]	11 serum potassium levels
RLY5016-301					
Part A: Single-blind, single-arm, patiromer treatment period, dose titration; Part B: Single-blind, placebo-controlled, parallel group, randomized withdrawal period	Starting dose of 8.4g or 16.8g per day (as divided doses BID); Titration range: 0g to 50.4g	4 week treatment period (Part A) followed by 8 week randomized placebo withdrawal period (Part B)	Hyperkalemia CKD patients receiving RAASi	243 adult patients enrolled in Part A 151 patients enrolled in Part B	14 serum potassium levels

Abbreviations:
BID = twice daily, CKD = chronic kidney disease, PD = pharmacodynamics,
QD = once daily
* expected number of samples per patient
[a] The 305 subjects reported here includes one subject ((b) (6)) with a false dose record and observation on Day 0. This subject was excluded from the previous CSR (304 subjects).
Source code: study-summary.R
Source file: study-summary-all.tex

Source: Applicant's PopPD report , Page 19 (link).

Table 12: PD model: Pharmacodynamic data summary of participants (number) and observations (number and percent) for participants receiving at least one dose of patiromer stratified by study.

	Number			Percent
Study	SUBJ	MISS	OBS	OBS
RLY5016-205	305	0	7119	71.2
RLY5016-206p	23	0	337	3.4
RLY5016-301	243	0	2543	25.4
All data	571	0	9999	100.0

SUBJ: subjects
MISS: missing observations (non-BLQ)
OBS: observations
BLQ: below limit of quantification
The 305 subjects reported in Study RLY5016-205 here differs than the number of subjects reported in the CSR (N = 304), because this analysis included one subject ((b) (6) that was found to have false dose record at Day 0.

Source: Applicant's PopPD report , Page 36 (link).

Table 13: PD model: Maximum dose summary for participants (number and percent) receiving at least one dose of patiromer stratified by study.

Study	Maximum Dose (g/day)	N Subjects	Percent of Study
RLY5016-205	8.4	36	11.8
	16.8	76	24.92
	25.2	92	30.16
	33.6	53	17.38
	42	16	5.25
	50.4	32	10.49
RLY5016-206p	4.2	4	17.39
	6	2	8.7
	8	4	17.39
	8.4	5	21.74
	12	3	13.04
	12.6	1	4.35
	16.8	2	8.7
	25.2	2	8.7
RLY5016-301	8.4	42	17.28
	16.8	96	39.51
	25.2	65	26.75
	33.6	33	13.58
	42	4	1.65
	50.4	3	1.23

Source: Applicant's PopPD report , Page 43 (link).

Table 14: Summary of Baseline Demographic Covariates for Analysis

	Study:			
	RLY5016-205 n = 305	RLY5016-206p n = 23	RLY5016-301 n = 243	Summary n = 571
Sex				
Female	112 (36.7)	9 (39.1)	103 (42.4)	224 (39.2)
Male	193 (63.3)	14 (60.9)	140 (57.6)	347 (60.8)
Race				
White	305 (100.0)	23 (100.0)	239 (98.4)	567 (99.3)
Black or African American	0 (0.0)	0 (0.0)	3 (1.2)	3 (0.5)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)
History of heart failure				
Yes	105 (34.4)	0 (0.0)	102 (42.0)	207 (36.3)
No	200 (65.6)	23 (100.0)	141 (58.0)	364 (63.7)
History of myocardial infarction				
Yes	0 (0.0)	0 (0.0)	60 (24.7)	60 (10.5)
No	305 (100.0)	23 (100.0)	183 (75.3)	511 (89.5)
Adult type 2 diabetes				
Yes	305 (100.0)	0 (0.0)	139 (57.2)	444 (77.8)
No	0 (0.0)	23 (100.0)	104 (42.8)	127 (22.2)
Any concomitant RAASI drugs				
Yes	288 (94.4)	16 (69.6)	243 (100.0)	547 (95.8)
No	17 (5.6)	7 (30.4)	0 (0.0)	24 (4.2)
Specific concomitant RAASI drugs				
Spironolactone	7 (2.3)	0 (0.0)	18 (7.4)	25 (4.4)
Losartan	83 (27.2)	1 (4.3)	42 (17.3)	126 (22.1)
Spironolactone, Losartan	17 (5.6)	0 (0.0)	2 (0.8)	19 (3.3)
No	198 (64.9)	22 (95.7)	181 (74.5)	401 (70.2)

Variable	n	Mean	Median	SD	Min / Max
Study: RLY5016-205					
Age (years)	305	66.3	68.0	8.59	37.0 / 80.0
Weight (kg)	305	86.4	86.0	12.7	53.5 / 133
eGFR (mL/min/1.73m^2)	305	33.1	33.1	13.2	8.53 / 94.3
Study: RLY5016-206p					
Age (years)	23	12.0	12.0	3.78	6.00 / 17.0
Weight (kg)	23	40.4	38.0	16.7	17.0 / 76.4
eGFR (mL/min/1.73m^2)	23	35.3	36.4	17.9	6.67 / 75.0
Study: RLY5016-301					
Age (years)	243	64.2	65.0	10.5	29.0 / 80.0
Weight (kg)	243	82.2	81.5	14.8	40.2 / 134
eGFR (mL/min/1.73m^2)	243	28.6	26.4	11.6	10.4 / 80.2
All data					
Age (years)	571	63.2	66.0	14.1	6.00 / 80.0
Weight (kg)	571	82.8	83.5	16.4	17.0 / 134
eGFR (mL/min/1.73m^2)	571	31.3	30.4	13.0	6.67 / 94.3

Note:
n: number of records summarized

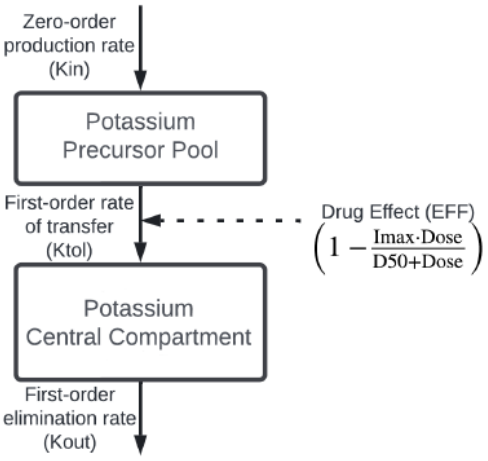
RAASi included the following drugs: benazepril, enalapril, enalaprilat, fosinopril, captopril, cilazapril, delapril, lisinopril, imidapril, moexipril, perindopril, ramipril, quinapril, spirapril, trandolapril, zofenopril, azilsartan, candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, eprosartan, spironolactone, eplerenone, finerenone, canrenone
The 305 participants reported in Study RLY5016-205 here differs from the number of participants reported in the CSR (N = 304), because this analysis included one participant ((b) (6)) that was found to have false dose record at Day 0.

The baseline eGFR value was calculated from the serum creatinine measurement corresponding to the baseline flag in the source data (laboratory test results domain), and if the flag was absent for a participant, the earliest observation was taken.
Source: Applicant's PopPD report , Page 37,38 (link).

Base model

The potassium concentration-time course was described by an indirect response model driven by patiromer dose shown in Figure 4. This model assumed that response to patiromer occurred as potassium moved from the precursor to the central compartment, described by a first-order rate of transfer from the precursor compartment (Ktol). Drug effect was assumed to inhibit Ktol via a maximum effect (Emax) model. The precursor and central compartments were assumed to start at steady baselines (i.e., their physiological levels, change with time when drug was administered, and eventually return to baseline). The model was parameterized in terms of a zero-order production rate constant (Kin) to a precursor compartment, a transfer rate from the precursor to central compartment (Ktol), and a first order elimination rate constant (Kout) from the central compartment to describe the natural loss of potassium. The base model equations are show in Figure 5. While an Emax model was used, when fitting the model, it became clear that estimate for dose required for 50% of the effect (D50) was continually going to a very small number. Eventually, D50 was fixed to 0.1 g/day to mimic an on-off type drug effect where any dose resulted in a maximum effect. This approach was justifiable given the exploratory plots showed all participants appeared to have a maximal effect, regardless of dose level.

Figure 4: PD model schematic



Source: Applicant's PopPD report , Page 55 (link).

Figure 5: The base model equations

$$BASE_i = \theta_1 \cdot e^{(\eta_{1i})}$$

$$Kin = \theta_2$$

$$Ktol = \theta_3$$

$$\mathrm{TVImax} = \theta_4 + \eta_{2i}$$

$$Imax_i = \frac{1}{1 + e^{-e^{\mathrm{TVImax}}}}$$

$$D50 = \theta_5$$

θ1 through θ5 are estimated parameters describing the typical baseline potassium (BASE), Kin, Ktol, Imax and the dose required for D50, respectively. η1i , to η2i are the subject-level random effects in BASE and Imax, respectively, for individual i. The Kout and drug effect (EFF) were then defined as:

$$Kout_i = \frac{Kin}{BASE_i}$$

$$\mathrm{EFF}_i = 1 - \frac{\mathrm{Imax} \cdot \mathrm{Dose}}{D50 + \mathrm{Dose}}$$

Dose was defined as the total daily patiromer dose (g/dose) and was time-varying to account any dose-titration occurring within a participant. The initial steady baselines of the precursor and central compartments were fixed to Kin_i /$Ktol_i$ (A_0(2) = Kin/Ktol, A_0(2): the potassium concentration in the initial potassium precursor compartment under steady state without treatment) and $BASE_i$ (A_0(1) = BASE, A_0(1): the potassium concentration in the potassium central compartment under steady state without treatment), respectively. The derivative equations are as following, in which A(1) is the potassium central compartment and A(2) is the potassium precursor compartment.

DADT(1) = Ktol * EFF * A(2) - Kout * A(1)
DADT(2) = Kin - Ktol * EFF * A(2)

Source: Applicant's PopPD report , Page 25, 26, 107 (link).

Reviewer's comments:
If D50 were fixed to be 0.1 g/day, the drug effect (EFF) is almost a constant (about 1- Imax). Therefore, the efficacy will NOT be related with dosage. However, increased dosage resulted in a better efficacy. Thus, it is not reasonable to fix D50 value to be 0.1 g/day for inhibition models.

The first-order conditional estimation (FOCEI) method was used to estimate population and individual model parameters, in which the 95% CIs of parameter estimates were derived from the covariance matrix of the estimates.

The inter-subject variability distributions used an exponential variance model for BASE and a logit transformation for Imax.

The residual error model included an additive error term, with an interindividual variance parameter (estimated using an exponential variance model), to estimate a residual variance error for each individual.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria, goodness-of-fit, a decrease in the minimum objective function value (OFV), successful model convergence, and diagnostic visual predictive check (VPC).

Covariate analysis

Covariates screened for inclusion in the PD model were based on mechanistic plausibility, exploratory analysis, and clinical interest, which are age, sex, baseline body size (body weight, body mass index (BMI)), baseline estimated glomerular filtration rate (eGFR), baseline creatinine, concomitant medication (i.e., RAASi), and disease status at enrollment (i.e., T2DM, myocardial infarction, and heart failure).

Software and estimation methods

Data manipulation, visualization, and simulations were conducted using R version 4.1., a data analysis language suitable for use in regulated environments. Population PD analyses were conducted using NONMEM® version 7.5 (ICON PLC, Ireland).

6.1.2.4 Final Model

The parameter estimates for the final PopPD model are listed in Table 15. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 6. The VPC plot for the final covariate model with all data is shown in Figure 7 stratified by maximum dose.

- The indirect response model with a precursor pool reasonably described changes in serum potassium in response to patiromer dosing.
- Age was included as a covariate in the model, while no changes in the structural model were required to describe pediatric patients when compared to adults.
- Covariates in the final model included RAASi concomitant medication (yes versus no), heart failure (yes versus no), myocardial infarction (yes versus no), type 2 diabetes (yes versus no), sex, (male versus female), age and baseline eGFR on both Imax and BASE.
- Although the baseline serum potassium slightly increased with increasing age, the magnitude of the patiromer effect on serum potassium concentration was consistent across adults, adolescents, and 6 to less than 12-year-old children.
- In the population simulations investigating serum potassium change from baseline in adults taking 8.4 g/day and pediatrics taking 4.2 g/day, distributions of change from baseline were generally similar across age groups, although a trend of increasing median change with increasing age was observed.
- A starting dose of 4.2 g/day for both pediatric cohorts is likely to yield patiromer effects that are comparable to those observed for the recommended 8.4 g/day starting dose in adult hyperkalemia patients. Further, given the limited difference in response across the range of

dose levels demonstrated by the population simulations, it is considered that a 4 g/day patiromer dose is likely to yield an equivalent effect to 4.2 g/day.

Table 15. Population PD Parameter Estimates for Final Models

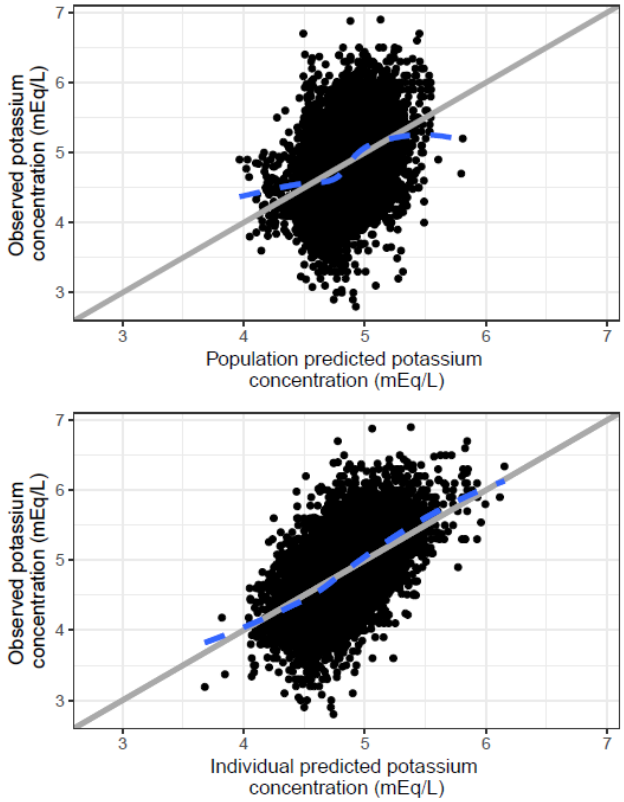
			Estimate	95% CI
Structural model parameters				
BASE (mEq/L)	θ_1	Baseline potassium	5.04	4.91, 5.16
Kin (mEq/(L*day))	θ_2	Zero-order production rate constant	0.0246	0.0225, 0.0267
Ktol (1/day)	θ_3	First-order rate of transfer from the precursor compartment	0.0499	0.0414, 0.0583
Imax	θ_4	Maximal inhibitory effect	1.36	0.771, 1.94
D50 (g/day)	θ_5	Dose required for 50% of the effect	0.100	FIXED
Covariate effect parameters				
Imax ~ CMALL	θ_7	RAASI concomitant medication effect on Imax	0.0980	-0.309, 0.505
BASE ~ CMALL	θ_8	RAASI concomitant medication effect on BASE	1.01	0.991, 1.03
Imax ~ HFF	θ_9	Heart failure effect on Imax	0.00134	-0.193, 0.196
BASE ~ HFF	θ_{10}	Heart failure effect on BASE	1.00	0.991, 1.01
Imax ~ MI	θ_{11}	Myocardial infarction effect on Imax	0.782	0.387, 1.18
BASE ~ MI	θ_{12}	Myocardial infarction effect on BASE	1.03	1.01, 1.05
Imax ~ T2DM	θ_{13}	Type 2 diabetes effect on Imax	-1.18	-1.53, -0.825
BASE ~ T2DM	θ_{14}	Type 2 diabetes effect on BASE	0.969	0.956, 0.983
Imax ~ Sex	θ_{15}	Sex (male) effect on Imax	-0.0167	-0.212, 0.179
BASE ~ Sex	θ_{16}	Sex (male) effect on BASE	1.00	0.990, 1.01
Imax ~ Age	θ_{17}	Age effect on Imax	0.423	0.134, 0.711
BASE ~ Age	θ_{18}	Age effect on BASE	-0.0366	-0.0501, -0.0230
Imax ~ EGFR	θ_{19}	EGFR effect on Imax	-0.274	-0.487, -0.0610
BASE ~ EGFR	θ_{20}	EGFR effect on BASE	-0.0201	-0.0308, -0.00952

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-BASE	$\Omega_{(1,1)}$	0.00198 [CV%=4.45]	0.00168, 0.00227	12.2
IIV-Imax	$\Omega_{(2,2)}$	0.444 [SD=0.110]	0.322, 0.565	35.9
IIV-RUV	$\Omega_{(3,3)}$	0.0612 [CV%=25.1]	0.0510, 0.0714	16.1
Interindividual covariance parameters				
Imax-BASE	$\Omega_{(2,1)}$	0.0154 [Corr=0.519]	0.0101, 0.0207	-
Residual variance				
Additive	θ_6	0.153	0.145, 0.161	-

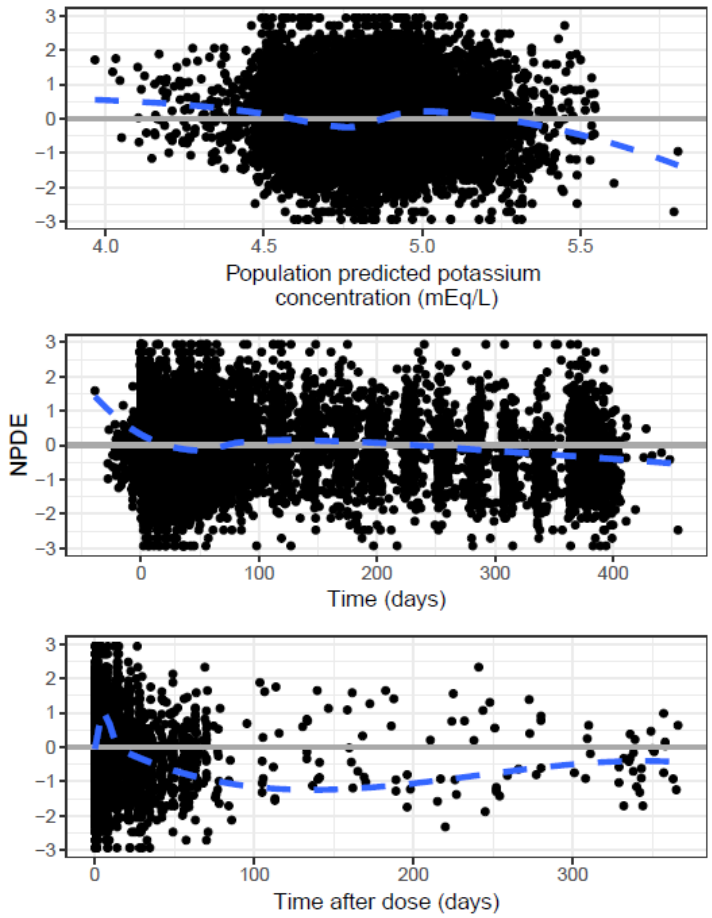
Parameters estimated in the logit-domain were back-transformed for clarity
Abbreviations: CI = confidence intervals; EGFR: estimated glomerular filtration rate
RAASI: renin-angiotensin-aldosterone-system inhibitor; SE: standard error
Confidence intervals = estimate ± 1.96 · SE
Corr: correlation coefficient; CV: coefficient of variation; SD: standard deviation; RUV: residual unexplained variability
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100

Source: Applicant's PopPD report , Page 48, 49 (link).

Figure 6. Goodness-of-fit plots for final covariate model



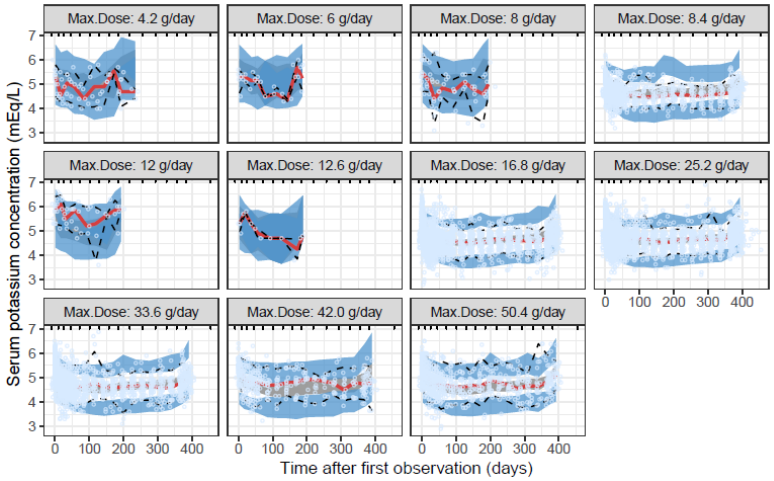
Observed values are indicated by solid black circles. The line of identity (solid grey) is included as a reference (x=y). The dashed blue line represents a LOESS smooth through the data.



Solid black circles represent the individual normalized prediction distribution errors (NPDE) values associated with each observation record. The solid horizontal grey line (residual = 0) was included for reference. The dashed blue line represents a LOESS smooth through the data.

Source: Applicant's PopPD report , Page 72, 73 (link).

Figure 7: VPC Stratified by maximum dose



Source: Applicant's PopPD report , Page 98 (link).

Reviewer's independent assessment
The concomitant RAASi, heart failure and sex on base and Imax, and eGFR on Imax were assessed, showing that covariates RAASi, heart failure and sex on base and Imax, and eGFR on Imax cannot be identified to be statistically significant, shown in Table 16. Moreover, if final model with estimated D50 (1.51 g/day) rather than fixed value (0.1 g/day), the model has lower OFV (objective function value). Meanwhile, although there is no obvious difference between parameter estimates between Applicant's final model with estimated D50 and model 5 (without RAASi, heart failure and sex on base and Imax, and without eGFR on Imax with estimated D50), Applicant's final model with estimated D50 has higher standard errors than model 5. Therefore, model 5 was used for simulation to evaluate pediatric starting dosage.

Table 16: Covariates Assessment

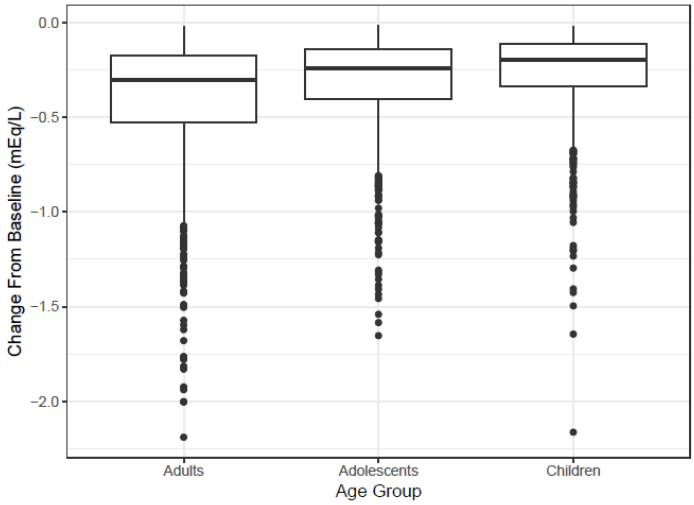
Model	OFV	Δ OFV
Applicant's Final model with fixed D50	-7165.456	0
Applicant's Final model with estimated D50	-7177.948	-12.492
Model without RAASi, heart failure and sex on base and Imax, and without eGFR on Imax with fixed D50	-7157.486	7.97
Model without RAASi, heart failure and sex on base and Imax, and without eGFR on Imax with estimated D50 (Model 5)	-7169.396	-3.94

Source: reviewer independent assessment

6.1.2.5 Simulation

Simulations from the final population PK model were employed to enable judgment about the clinical relevance of the covariates identified in the model development process. Potassium concentration-time profiles were derived from model predictions for a reference female subject without RAASi, heart failure, history of myocardial infarction, type 2 diabetes and with an estimated eGFR of 30.4 mL/min/1.73 m^2. The model-predicted change from baseline of potassium concentration time-profiles stratified by age groups (dosage: adult 8.4 g/day, pediatric 4.2 g/day) after one year treatment was shown in Figure 8, which showed that a trend of increasing median change with increasing age was observed. Model-predicted change from baseline serum potassium concentration stratified by dose groups for pediatric patients 12 to <18 years of age is shown in Figure 13, which showed that a 4 g/day patiromer dose yields an equivalent effect to 4.2 g/day. Therefore, the pharmacodynamic model supports the recommended starting dose of 4 g/day in pediatric patients 12 to <18 years of age.

Figure 8: PD Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group at one year.



Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5*IQR.
Source: Applicant's PopPD report , Page 94 (link).

Reviewer's Independent Assessment
Based on Applicant's simulation datasets and codes, the change from baseline of serum potassium concentration and the percentage of serum potassium concentration in the range of 3.8 mEq/L and 5 mEq/L after one year treatment was calculated shown in Table 17, which showed a trend of increasing median or mean change with increasing age. Meanwhile the change from baseline of serum potassium concentration and the percentage of serum potassium concentration in the range of 3.8 mEq/L and 5 mEq/L at day 1, day 7, day 14, week 14, week 22 and week 26 treatment were evaluated and shown in Table 18, Table 19*, Table* 20*, Table* 21*, Table* 22*, and Table* 23 *, respectively. The plots of simulations for 1000 participants in each age group of serum potassium concentration, change from baseline in serum potassium and percentage of participants with serum potassium concentration in range of 3.8 to 5 mEq/L at week 1, 2, 14, 22, 26, 52 with once daily dose 8.4 g for adults and 4.2 g for pediatrics were shown in Figure 9, Figure* 10*, Figure* 11*, and Figure* 12*, respectively, which have a similar trend among adults, adolescence (age:12 to <18) and pediatrics(6 to <12) and efficacy of adults is better than those of adolescence (age:12 to <18) and pediatrics(6 to <12).*

In Cohort 2 (6 to <12 years of age), the primary efficacy endpoint, the change in serum potassium from baseline to day 14, was NOT achieved.[3] *Therefore, the starting dose for pediatrics (age: 6 to <12) was not assessed.*

In Cohort 1, model-predicted pediatric (age: 12 to <18) change in serum potassium from baseline to day 14 stratified by dose groups showed that a 4 g/day patiromer starting dose yields a comparable efficacy as 4.2 g/day patiromer starting dose (Figure 13). Therefore, the Applicant's recommended starting dose of 4 g/day for pediatrics (12 to <18), which can be titrated based on monitored serum potassium level [4]*, is acceptable.*

[3] Labeling, page 12 (link)
[4] Labelling page 2 (link)

Table 17: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group at one year

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.324	-0.3	-0.83	-0.03	59.7	[-0.334, -0.314]
Age 12 to < 18	-0.18	-0.175	-0.403	-0.018	16.6	[-0.184, -0.175]
Age 6 to <12	-0.167	-0.161	-0.433	-0.019	7.4	[-0.171, -0.162]

Source: reviewer independent assessment

Table 18: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group at the first days

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	0	0	0	0	10.6	[0, 0]
Age 12 to <18	0	0	0	0	5.6	[0, 0]
Age 6 to <12	0	0	0	0	2.1	[0, 0]

Source: reviewer independent assessment

Table 19: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group after 7 days

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.111	-0.115	-0.141	-0.04	21.9	[-0.112, -0.11]
Age 12 to< 18	-0.092	-0.095	-0.119	-0.024	10.1	[-0.093, -0.091]
Age 6 to <12	-0.088	-0.091	-0.121	-0.025	4.8	[-0.089, -0.087]

Source: reviewer independent assessment

Table 20: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group after 14 days

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.208	-0.214	-0.269	-0.07	37.4	[-0.21, -0.206]
Age 12 to <18	-0.169	-0.174	-0.223	-0.042	16.8	[-0.171, -0.167]
Age 6 to <12	-0.161	-0.167	-0.228	-0.044	9.2	[-0.163, -0.158]

Source: reviewer independent assessment

Table 21: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group after 14 weeks

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.676	-0.687	-1.11	-0.122	94.2	[-0.689, -0.664]
Age 12 to <18	-0.466	-0.474	-0.765	-0.068	64.5	[-0.475, -0.457]
Age 6 to <12	-0.433	-0.441	-0.797	-0.072	45.3	[-0.442, -0.424]

Source: reviewer independent assessment

Table 22: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group after 22 weeks

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.664	-0.663	-1.235	-0.094	92.6	[-0.678, -0.649]
Age 12 to <18	-0.423	-0.426	-0.769	-0.053	57.1	[-0.432, -0.414]
Age 6 to <12	-0.391	-0.393	-0.809	-0.056	37.2	[-0.4, -0.382]

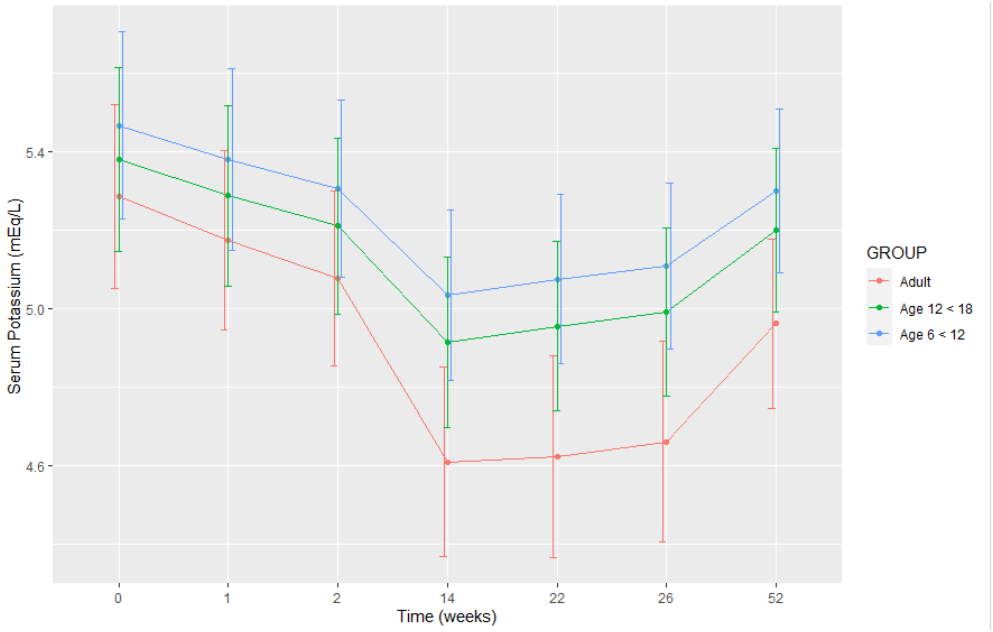
Source: reviewer independent assessment

Table 23: Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group after 26 weeks

GROUP	mean	median	min	max	Percentage of Potassium in range of [3.8 , 5] mEq/L	95% CI
Adults	-0.626	-0.619	-1.231	-0.081	90.2	[-0.64, -0.611]
Age 12 to <18	-0.387	-0.386	-0.732	-0.046	52.1	[-0.396, -0.379]
Age 6 to <12	-0.357	-0.356	-0.773	-0.048	30.6	[-0.366, -0.348]

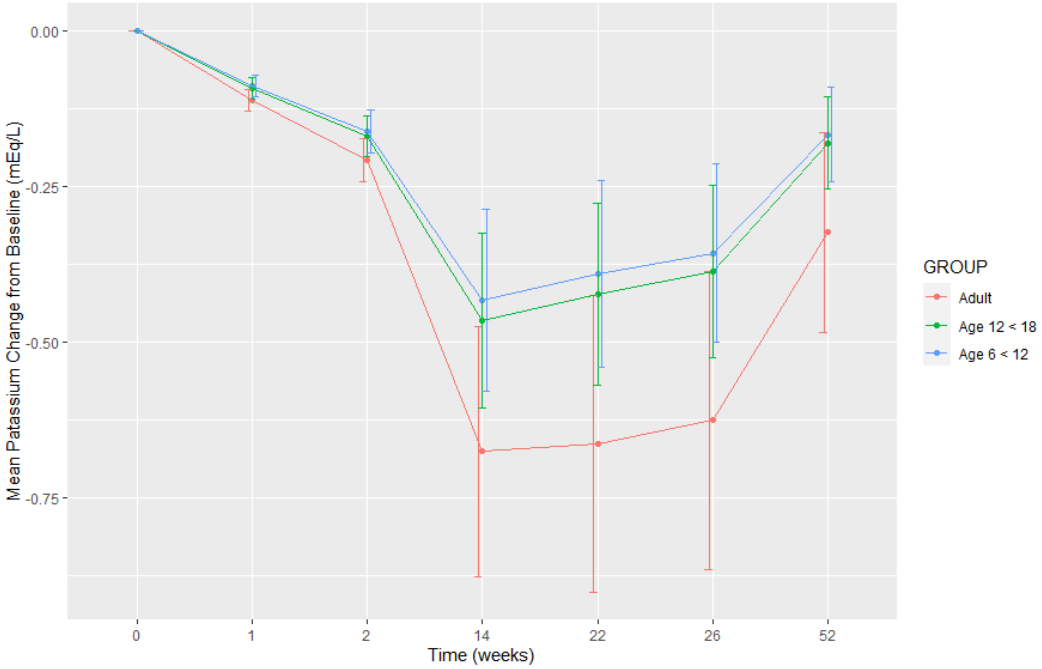
Source: reviewer independent assessment

Figure 9: Simulations for 1000 participants in each age group: serum potassium concentration (mean with standard deviation) at week 1, 2, 14, 22, 26, 52 with once daily dose 8.4 g for adults and 4.2 g for pediatrics



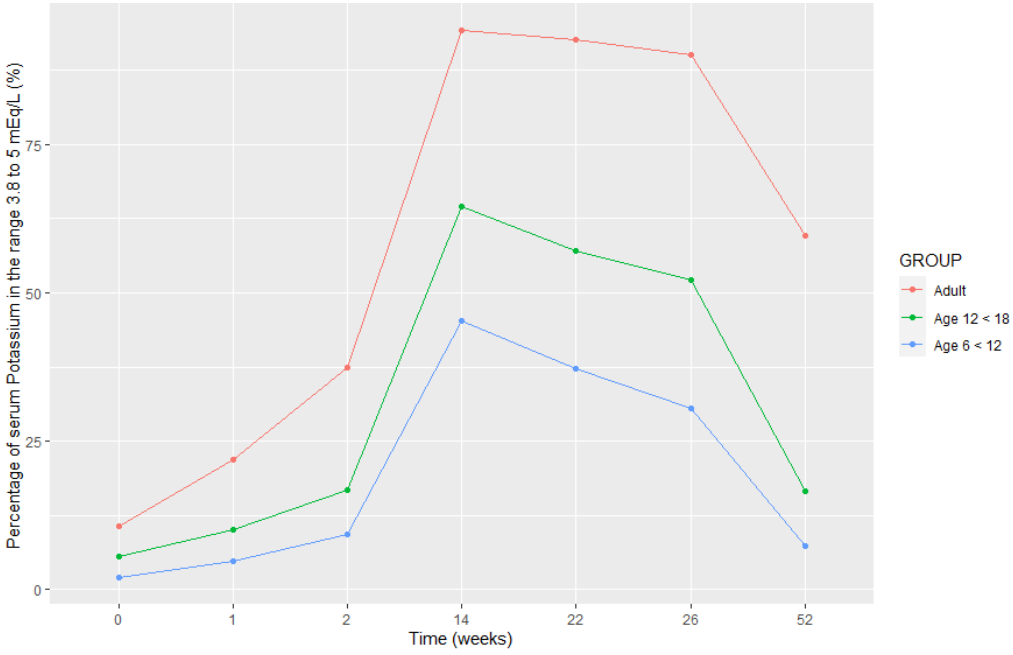
Source: reviewer independent assessment

Figure 10: Simulations for 1000 participants in each age group: change from baseline in serum potassium (mean with standard deviation) at week 1, 2, 14, 22, 26, 52 with once daily dose 8.4 g for adults and 4.2 g for pediatrics



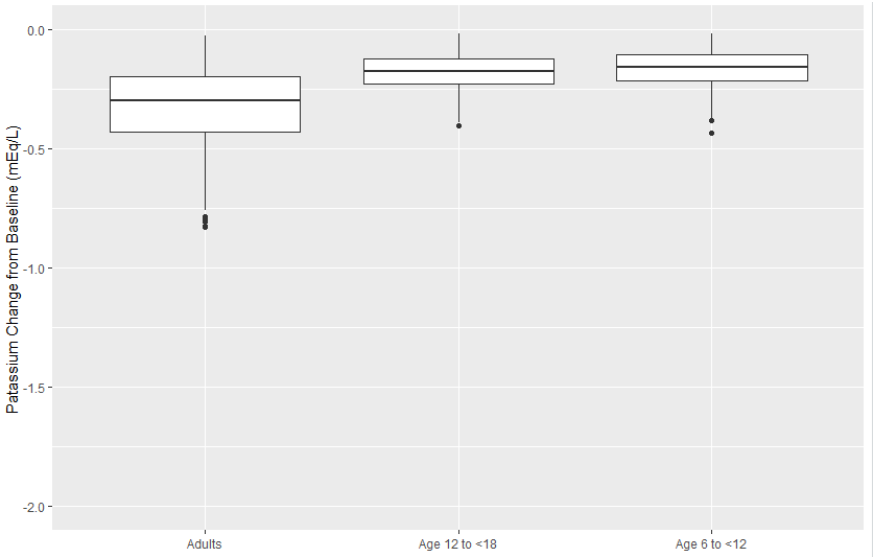
Source: reviewer independent assessment

Figure 11: Simulations for 1000 participants in each age group: Percentage of participants with serum potassium concentration in range of 3.8 to 5 mEq/L at week 1, 2, 14, 22, 26, 52 with once daily dose 8.4 g for adult and 4.2 g for pediatrics



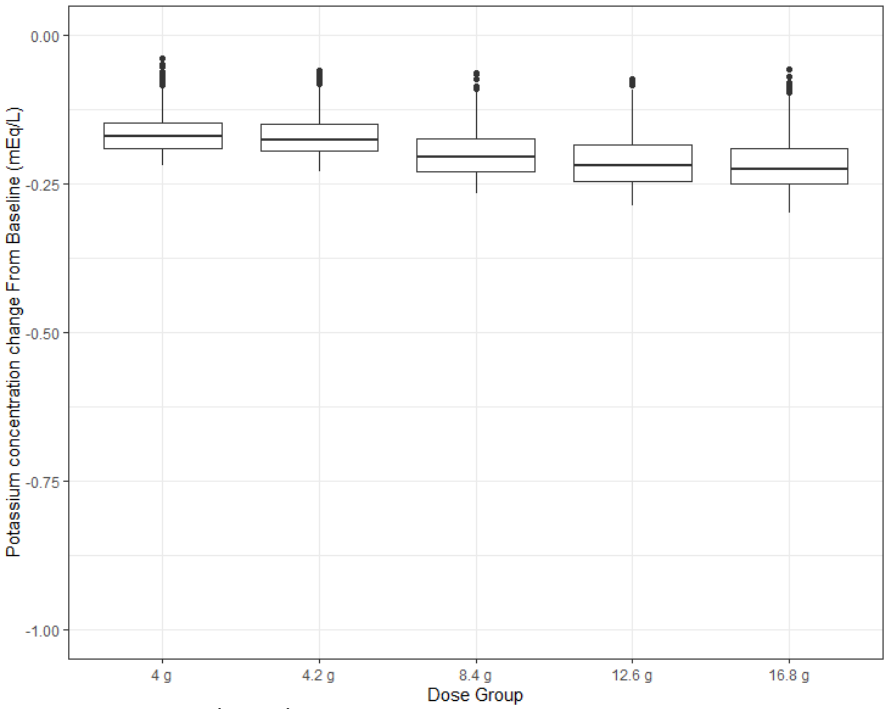
Source: reviewer independent assessment

Figure 12: PD Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration for 1000 participants in each age group at one year.



Source: reviewer independent assessment

Figure 13: PD Final Model Population Simulations: Summary of individual simulated mean change from baseline serum potassium concentration to day 14 for 12 to <18-year-old patients (n=1000 in each dose group)



Source: reviewer independent assessment

6.2 Human Participants Protections/Clinical Site and Other Good Clinical Practice Inspections/ Financial Disclosure

FDA Inspections: FDA did not request inspections of clinical investigator sites based on review of financial disclosures and consistency of the primary endpoint findings after excluding one site in the Ukraine (7903) that enrolled the most patients. Site 7903 enrolled 6 patients (2 in Cohort 1 and 4 in Cohort 2).

Site Audits and Data Quality Assurance: The Applicant's Quality Assurance department (or representative) monitored the study and conducted investigator site audits to ensure the accuracy and reliability of clinical study data. Audits included, but were not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Audits were conducted on three sites (3912, 7903, and 7904).

According to the RLY5016-206p (EMERALD) Clinical Study Report, electronic case report forms (eCRFs) were completed from source documents by study personnel and were source-document verified for accuracy and completeness by the clinical monitor.

Financial Disclosures: The Applicant has adequately disclosed financial arrangements with clinical investigators in EMERALD. None of the investigators had disclosable financial interests of >$25,000.

Table 24. Financial Disclosures

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 126 (37 principal investigators and 89 sub-investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: 2 (payments for consulting services, service on advisory boards, speaker fees, honoraria, research support, donation to a research consortium, and payment for laboratory audits) Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

6.3 Review Team

Table 25. Review Team

Role (Office/Division)	Name(s)
Regulatory Project Manager (OCHEN/DRO-CHEN)	Sabry Soukehal, RAC, DCPM
Clinical Pharmacology Reviewer (OCP/DCEP)	Anusha Ande, PhD
Clinical Pharmacology Team Leader (OCP/DCEP)	Harisudhan Thanukrishnan, PhD
Pharmacometrics Reviewer (OCP/DPM)	Hezhen Wang, PhD
Pharmacometrics Team Leader (OCP/DPM)	Hao Zhu, PhD
Clinical Reviewer (OCHEN/DCN)	Kirtida Mistry, MBBCh, DCH, MRCPCH
Associate Director for Labeling (OCHEN/DCN)	Michael Monteleone, MS, RAC
Deputy Division Director (OCHEN/DCN)	Aliza Thompson, MD, MS

OCHEN=Office of Cardiology, Hematology, Endocrinology, and Nephrology
OCP=Office of Clinical Pharmacology
DCN=Division of Cardiology and Nephrology
DCEP=Division of Cardiometabolic and Endocrine Pharmacology
DPM=Division of Pharmacometrics
DRO-CHEN=Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

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/s/

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