CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205739Orig1s000

OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	October 21, 2015
From	Ellis F. Unger, MD, Director, Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	205739
Applicant Name	Relypsa, Inc.
Date of Submission	October 21, 2014
PDUFA Goal Date	October 21, 2015
Proprietary Name/ Established (USAN) Name	Veltassa patiromer (patiromer sorbitex calcium)
Dosage Forms/Strengths	Oral suspension/packets containing 8.4, 16.8, or 25.2 grams patiromer
Indication:	Treatment of hyperkalemia
Action:	**Approval**

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Sabry Soukehal
Medical Officer Clinical Review	Shen Xiao MD, PhD
Clinical Pharmacology/Pharmacometrics	Ju-Ping Lai, PhD; Jeffry Florian, PhD; Rajanikanth Madabushi PhD
Statistical Review	Fanhui Kong, PhD; Hsien Ming Hung, PhD
Pharmacology Toxicology	William Link, PhD; Al De Felice, PhD
Office of New Drug Quality Assessment	Raymond Frankewich, PhD; Mohan Sapru, PhD; Kasturi Srinivasachar, PhD; Vipul Dholakia; Erika Pfeiler; Michael Trehy; Ilan Geerlof-Vidavsky; Cindy Diem Ngo; Xiaofei Liu; Michael Folkendt; Raanan Bloom; Elsbeth Chikhale, PhD; Angelica Dorantes, PhD
Office of Scientific Investigations	Sharon K. Gershon PharmD; Susan Thompson, MD; Kassa Ayalew, MD, MPH
Division of Pediatric and Maternal Health	Not applicable
Biopharmaceutics Review	Reviewers now part of Office of New Drug Quality Assessment because of reorganization
Division of Medical Policy Programs	Karen Dowdy, RN, BSN; Shawna Hutchins, MPH, BSN, RN; LaShawn Griffiths, MSHS-PH, BSN, RN
Office of Prescription Drug Promotion	Puja Shah, PharmD
Division of Medication Error Prevention and Analysis	Janine Stewart, PharmD; Chi-Ming (Alice) Tu, PharmD
Risk Management Review	Not applicable (Leah Hart and Kim Lehrfeld were involved during the DDI discussions but they did not provide a review in DARRTS)
Carcinogenicity Study	Not applicable
Executive Cancer Assessment Committee	Not applicable
Cross-Discipline Team Leader	Aliza Thompson, MD
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge, MD, PhD

1. Introduction

Relypsa, Inc. is seeking approval of patiromer, a new molecular entity, for the proposed indication: "Veltassa (patiromer) is indicated for the treatment of hyperkalemia."

With a number of changes to the label, the review team endorses approval, and I agree with their recommendation.

2. Background

Description:

Patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon, thereby increasing fecal potassium excretion and decreasing serum potassium. Patiromer will be supplied as a powder for suspension in water for oral administration. The drug will be packaged in single-use packets containing 8.4, 16.8, or 25.2 grams patiromer.

Disease Background:

Hyperkalemia is typically defined as a serum potassium > 5 mEq/L. The extracellular concentration of potassium is tightly regulated by the movement of transcellular potassium and urinary excretion. Thus, hyperkalemia is rare in the general population. In patients with acute or chronic kidney disease or heart failure, particularly those who are taking renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors, i.e., angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists), various degrees of hyperkalemia are not unusual. Mild to moderate hyperkalemia is typically asymptomatic. Marked elevations in serum potassium levels can cause cardiac arrhythmias (sometimes fatal), cardiac conduction abnormalities, muscle weakness, and paralysis. Treatment options for the management of hyperkalemia are limited, and well summarized by Dr. Xiao (see page 12 of his review). Sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. Use of SPS is generally limited to the acute setting because of tolerability and safety concerns (i.e., rare colonic necrosis; exchange of potassium for sodium, leading to volume overload or hypernatremia).

Regulatory History:

The regulatory history is extremely well documented in Dr. Xiao's review (pp 13-16). His description suggests a high degree of collaboration between the Division/Office and the applicant. For the phase 3 study, the Division initially issued a no agreement letter for the applicant's special protocol assessment, but with collaboration with the Division and revision of the protocol, the phase 3 study was carried out under a special protocol agreement.

3. Product Quality

OPQ recommends approval from a drug product perspective.

There were originally issues related to elemental impurities in the drug substance and xanthan gum, including acceptance criteria, analytical procedures, and validation reports. After considering additional information provided by the applicant, the OPQ reviewers determined that

the product complies with the requirements for Class (b) (4) elemental impurities as specified in ICH Guidelines.

From a Quality perspective, a major issue is that the drug generates fluoride ion upon degradation. According to the Quality review, this risk can be adequately addressed by long-term storage in the refrigerator (i.e., at 2°C to 8°C).

Drug Substance: The drug substance is a free flowing powder composed of individual spherical beads (b) (4) (b) (4)

Patiromer refers to the USAN for the (b) (4) The drug (b) (4) as the anion, the active moiety, with calcium-sorbitol as the counterion. The established name for the active moiety is "patiromer" and for the drug substance is "patiromer sorbitex calcium." Patiromer will be supplied as a powder for oral suspension in water in 3 strengths. An actual taste test confirmed that the powder was bland without an objectionable taste (I was a tester; in my opinion, the drug had no flavor).

Drug Product: The product formulation is (b) (4)% drug and (b) (4)% xanthan gum (b) (4) The drug product is supplied in single-use packets to be mixed with water.

Expiration Date and Storage Conditions: The drug product is stable at 2-8°C (b) (4) (b) (4) Based on the available data, a 24-month drug product expiration date is being granted when stored in the refrigerator at 2 to 8°C (36 to 46°F). In-use stability studies support storage at room temperature for up to 3 months.

Of note, prior to approval and finalization of labeling, the applicant packaged their product in anticipation of a rapid launch. Although the cartons were properly labeled, the drug pouches inside the cartons carry a statement (b) (4) Because these are not the proper storage conditions to which OPQ agreed, this pre-printed labeling is unacceptable. Per a October 20, 2015 teleconference with OPQ and the Division, the applicant has agreed to take corrective action (b) (4) on all of the mislabeled packets prior to distribution. The applicant also agreed to correct the storage conditions with the next printing of the packets.

Facilities review/inspection: All inspections have been completed. The drug product and drug substance manufacturing facilities have been deemed acceptable.

4. Nonclinical Pharmacology/Toxicology:

The preclinical toxicology program was deemed to be well-conducted, thorough, and interpretable, with no issues precluding approval.

The applicant demonstrated that the drug is not absorbed from the gastrointestinal (GI) tract, binds potassium ions in the colon, and decreases serum potassium. Toxicity studies

demonstrated that the drug is essentially inert and non-toxic. The potential for drug-drug interactions was sufficiently characterized.

ADME studies: In radiolabeled ADME studies conducted in rats and dogs, there was no significant systemic absorption of patiromer. Quantitative whole-body autoradiography in rats showed that radioactivity was limited to the GI tract, with no detectable radioactivity in other tissues or organs.

Toxicity studies: No adverse effects were observed in repeat-dose toxicity studies in rats or dogs following oral administration. No target organ toxicity was identified in either species. In dogs, the NOAEL for RLY5016S administered in the daily diet for 39 weeks was > 3.75 g/kg/d (expressed as RLY5016).

Degradation: As previously noted, fluoride is generated as a degradation product. According to Dr. Link, fluoride that dissociates from the polymer would be expected to form CaF_2, an insoluble salt. A rat study conducted to assess the effect of administering the polymer anion with calcium vs. sodium as the counter-ion confirmed that systemic absorption of fluoride is substantially lower with the calcium salt, presumably because CaF_2 is far less soluble and less bioavailable than NaF.

Pharmacology: RLY5016 was found to bind potassium in ionic matricies *in vitro*, enhance fecal potassium excretion in animals with normal renal function, and decrease serum potassium levels in hyperkalemic rats with impaired renal function. The drug also binds other cations (e.g., H^+, Mg^{++}, Ca^{++}, and Na^+); the extent of binding depends on the local concentration of the cation and its valence. According to Dr. Link, the majority of K^+ binding to patiromer occurs in the colon where it is most abundant.

Reproductive toxicology: Reproductive and development toxicities were evaluated at the maximum feasible dosages in a rat fertility study, and rat and rabbit teratology studies. No effects were noted, beyond nutritionally-related effects on dams' offspring. As agreed with the Agency, a peri/postnatal development study was not performed.

Genotoxicity: Patiromer was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames assay). The drug was negative for inducing chromosomal aberrations in CHO cells. Patiromer was non-mutagenic in the rat micronucleus assay.

Carcinogenicity: Given that the drug is not absorbed, carcinogenicity testing was waived.

5. Clinical Pharmacology

The Clinical Pharmacology team recommends approval. As discussed in Section 4, the drug is not significantly absorbed; therefore, conventional PK studies were not performed. On the other hand, the Clinical Pharmacology team performed a number of analyses on the data from the phase 1, 2, and 3 studies to identify an optimal dosing scheme, as explained below.

Dosing regimen: The recommended starting dose of patiromer in the applicant's initial proposed label (b) (4)

(b) (4)

Based on the clinical pharmacology team's analyses of the data, however, and in light of the potential for drug-drug interactions, the clinical pharmacology team is recommending QD dosing (b) (4) and a starting dose of 8.4 g, irrespective of the baseline [K^+].

- Dosing frequency: A phase 1, open-label, multiple-dose, crossover study in healthy subjects provided support for the efficacy of a once-daily dosing regimen. Twelve (12) subjects received a total of 25.2 g patiromer daily for 6 days, administered as a QD, BID, or TID regimen. As shown in Table 1, adapted from the applicant's summary-clin-pharm-0002, the three regimens had similar effects on fecal and urinary potassium excretion. Thus, the data show that there was no advantage for administration of patiromer in divided doses.

Table 1: Effect of QD, BID and TID dosing on fecal potassium and urinary potassium excretion

Variable/Time Point	8.4 g TID (N=12)	12.6 g BID (N=12)	25.2 g QD (N=12)	Overall p-value
Fecal Potassium (mg)				
Baseline	584 ± 244	584 ± 244	584 ± 244	
Endpoint	2134 ± 629	2003 ± 661	1867 ± 540	0.37
Change from baseline to endpoint	1550 ± 519	1419 ± 550	1283 ± 530	0.37
Urinary Potassium (mg)				
Baseline	4450 ± 362	4450 ± 362	4450 ± 362	
Endpoint	3010 ± 474	2916 ± 327	3012 ± 446	0.39
Change from baseline to endpoint	-1440 ± 384	-1534 ± 295	-1438 ± 384	0.39

- Starting dose: The applicant had proposed a starting dose of (b) (4) In the Phase 2 study, RLY5016-205 (heretofore "Study 205"), in patients with chronic kidney disease and hyperkalemia (Cohort 3), Dr. Lai found that the decrease in serum [K^+] at Day 3 was not dose-related. At FDA's request, the applicant performed a mixed model repeated measures (MMRM) analysis of the integrated efficacy data from the phase 2 and 3 trials. The results also showed that baseline [K^+] played a much larger role in the change in [K^+] than the patiromer dose (see Table 2). Based on these and other considerations, the clinical pharmacology team recommended a starting dose of 8.4 g/day, regardless of the baseline serum [K^+].

Table 2: Model-projected mean change in serum potassium (mEq/L) based on baseline serum potassium and interval dose (Source: Table 1, Clinical Pharmacology Review)

Baseline Serum K (mEq/L)	Change from baseline serum K (mEq/L)			
	8.4 g/day	16.8 g/day	25.2 g/day	33.6 g/day
5.0	-0.19	-0.22	-0.26	-0.29
5.5	-0.49	-0.52	-0.56	-0.59
6.0	-0.78	-0.81	-0.85	-0.88

- Dose Titration: In the phase 3 trial, the patiromer dose was titrated to achieve a target [K^+] of 3.8 to < 5.1 mEq/L, based on assessments beginning on Day 3 and then weekly to the end of the 4-week treatment period. The phase 2 trial also permitted dose titration starting on Day 3.

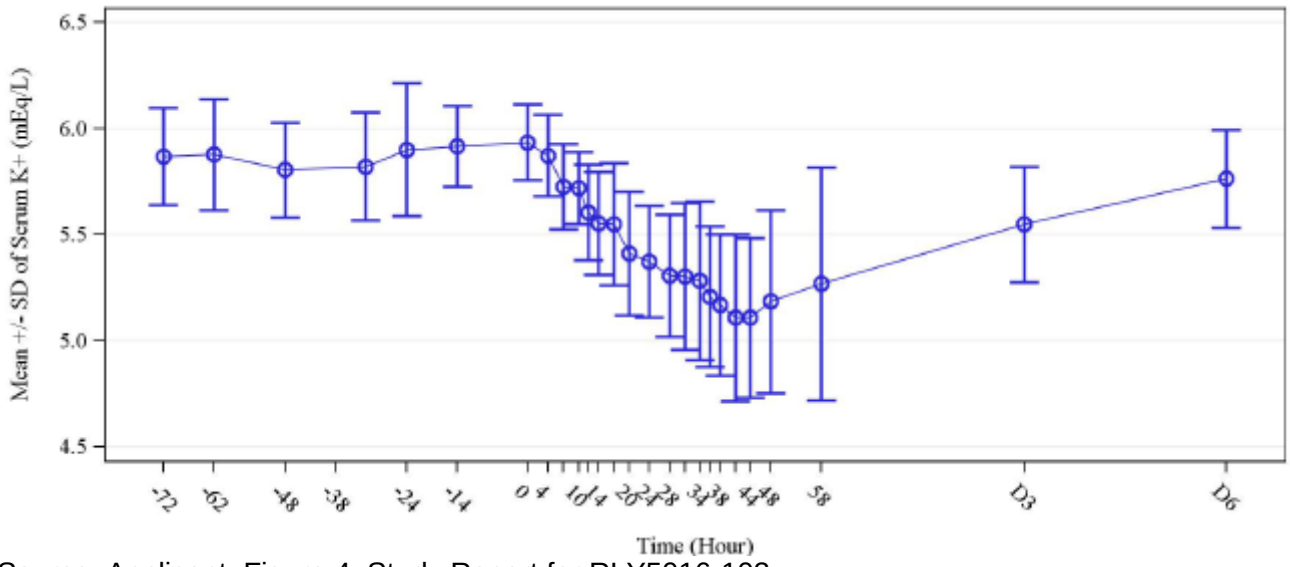
  Although analyses of the integrated data from the phase 2 and 3 trial did not show a convincing dose-response over the doses studied, the Clinical Pharmacology team showed, nevertheless, that some patients may ultimately need higher doses to achieve the desired target. Given that one cannot prospectively identify such patients, the team considered it reasonable to allow titration to higher doses.

  In terms of the interval for titration, dose titration was allowed as early as Day 3 in the phase 2 and 3 trials. As shown by the Clinical Pharmacology team, however, it takes longer than 3 days for [K^+] to reach equilibrium after a change in dose. Based on the available data on the time course of patiromer's effect, the label will suggest waiting at least 1 week prior to up-titration.

Time course of effect: The time to onset and offset of patiromer's effect was evaluated in an inpatient setting: an uncontrolled study (Study 103) in 25 hyperkalemic patients with chronic kidney disease (CKD) (mean baseline [K^+] = 5.9 mEq/L), where patients received a potassium-controlled diet. The study included a 3-day run-in period and a 2-day treatment period in which subjects received patiromer 8.4 grams BID (4 total doses in 2 days). Statistically significant reductions in serum potassium (-0.2 mEq/L) were first observed 7 hours after the first patiromer dose. Potassium levels continued to decline during the 48-hour dosing period. Potassium levels rose in the 4 days following discontinuation, as shown in Figure 1.

Importantly, given the many hours required for patiromer to travel to its site of action in the colon and reduce [K^+], the label will include a Limitation of Use statement to explain that the drug should not be used for the management of life-threatening hyperkalemia.

Figure 1: Mean and Standard Deviation of Central Laboratory [K^+] (mEq/L) Over Time



Source: Applicant, Figure 4, Study Report for RLY5016-103

QT effects: Because the drug product is not significantly absorbed, a thorough QT study was not performed.

Drug-drug interactions:

Patiromer's potential to bind other oral medications is a significant issue. Based on an assessment of patiromer's physicochemical characteristics, interactions are expected with cationic, anionic (due to the calcium-sorbitol counter-ion), and neutral (hydrophilic interaction) oral drugs when concomitantly administered.

The Office of Clinical Pharmacology believes that the risk can be adequately mitigated through once-daily dosing [redacted] (b) (4) and by separating administration of other drugs by ≥ 6 hours.

As has been the practice with oral phosphate binders, patiromer's potential to interact with oral medications was evaluated *in vitro*. Of the 28 drugs tested, approximately half showed an interaction (defined as >30% binding). (Rivaroxaban did not meet the 30% threshold, but was close [28%]). See Table 3.

Table 3: Patiromer's Drug-Drug Interaction Potential—Binding Based on *In Vitro* Testing (Source: From a CDER Regulatory Briefing, "Treatment of Hyperkalemia," September 18, 2015)

Allopurinol	Cinacalcet	Lisinopril	Rivaroxaban
Amlodipine	Ciprofloxacin	Lithium	Spironolactone
Amoxicillin	Clopidogrel	Metformin	Thiamine
Apixaban	Digoxin	Metoprolol	Trimethoprim
Aspirin	Furosemide	Phenytoin	Valsartan
Atorvastatin	Glipizide	Quinidine	Verapamil
Cephalexin	Levothyroxine	Riboflavin	Warfarin
Key:	> 50% binding	30 to 50% binding	28% binding

The applicant proposed an approach to separate the time of dosing of patiromer and other orally administered medications by (b) (4) hours based on time of gastric emptying. Although the concept of considering time to gastric emptying as a guide to spacing drug administration seemed sensible, the Clinical Pharmacology review team did not deem (b) (4) hours to be adequate. The review team filed a review addendum concluding that a 6-hour separation would be sufficient, and this information was communicated to the applicant in a General Advice Letter on September 16, 2015.

The Clinical Pharmacology review team considers the critical factors for determining the separation time required to mitigate drug-drug interactions to be: 1) GI motility; and 2) the time required for maximum or near-maximum absorption of co-medications, i.e., their T_{max}.

GI motility can be described by GI transit time, which includes gastric emptying time and intestinal and colonic transit times. Gastric emptying time (GET) is defined as the time between

ingestion and stomach emptying, the time of relaxation of the pyloric sphincter. Gastric emptying time is highly variable and depends upon the type, size, and frequency of meals, as well as particle size, caloric value, posture, and stress. In addition, delayed gastric emptying is known to occur in various patient populations. For example, in patients with diabetic gastroparesis, GET has been found to be 50% longer than in healthy controls (5.4 vs. 3.6 hours). GET has also been reported to be 66% longer in patients on chronic hemodialysis. Although the Clinical Pharmacology review team could not identify dedicated studies characterizing GET for small particles or pellets in these patient populations, they considered a 2- to 6-hour range to constitute a reasonable approximation of GET for the target population.

Following gastric emptying, the small bowel transit time (SBTT) defines the time required for transit of chyme through the small intestine to the cecum. The SBTT is approximately 4 to 6 hours, and little dependent on the fasted vs. fed state, or disease states such as gastroparesis.

The time elapsed from arrival of chyme at the ileocecal junction until exit from the body is defined as colonic transit time (CTT). The CTT is prolonged in patients with gastroparesis. The review team noted, however, that prolongation of CTT is less of a concern with respect to interaction potential because drug absorption of most medications primarily occurs in the small intestine, with less absorption in the stomach and colon.

The other principal factor in determining the separation time required to mitigate drug-drug interactions is T_{max}.

For immediate-release products, T_{max} usually occurs within ~2 hours. For such products, a shorter separation time of 2 to 3 hours could be considered if the other medication is administered prior to patiromer. But 2 to 3 hours may not be adequate if patiromer is administered first.

For extended-release products, T_{max} is generally later, and shorter separation times cannot be considered. Release and absorption of extended-release drug products can occur throughout the small bowel.

The crux of the logic is that once gastric emptying occurs, movement through the small bowel occurs at approximately the same rate in all patients. Thus, a 6-hour separation of dosing will ensure that patiromer and other medications enter the small bowel at different times, limiting their physical contact and their potential for binding in the small (or large) intestine.

Thus, the review team concluded that a separation of at least 6 hours between administration of patiromer and other orally administered medications represents an adequate mitigation strategy that is simple and feasible, and can be applied to all medications.

A potential for interaction cannot be ruled out for products that are designed to be released in the colon, particularly when patiromer is administered prior to the other medication. Colonic release of drugs is generally reserved for suppositories or enemas, and prior patiromer administration could reduce the amount of these drugs available for absorption.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

The principal evidence of efficacy in lowering serum potassium levels is provided by trial RLY5016-301, heretofore "Study 301."

Design: Study 301 was a multi-center, phase 3 trial in patients with CKD (eGFR 15 to 60 mL/min/1.73m^2) and hyperkalemia at screening ([K^+] = 5.1 to < 6.5 mEq/L by local laboratory) who were on a stable dose of at least one RAAS inhibitor for at least 28 days.

The trial consisted of two parts: Part A, an uncontrolled, single-blind, 4-week, titration phase, and Part B, a single-blind, randomized withdrawal phase (only the subjects were blinded).

Subjects were initiated on patiromer 4.2 or 8.4 g BID, based on screening [K^+]. Starting on Day 3 of treatment, the dose could be titrated based on the local laboratory [K^+].

Subjects who met all of the following criteria were eligible for Part B, the randomized withdrawal phase: completion of Part A on a daily dose of 8.4 to 50.4 g patiromer; a Part A baseline [K^+] $\geq$ 5.5 mEq/L; and a local laboratory-measured [K^+] of 3.8 to < 5.1 mEq/L at the Week 4 visit of Part A while receiving a RAAS inhibitor.

In Part B, subjects who met the aforementioned entry criteria were randomized to continued treatment with patiromer or withdrawal of treatment, i.e., placebo for 8 weeks. Subjects randomized to patiromer continued on the same daily dose they had been on at the Part A Week 4 visit, with subsequent dose titration as needed.

The 1° efficacy endpoint for Part A was the change in [K^+] (central laboratory) from the Part A baseline to the Part A Week 4 visit. The 1° efficacy endpoint for Part B was the change in [K^+] (central laboratory) from the Part B baseline to either:

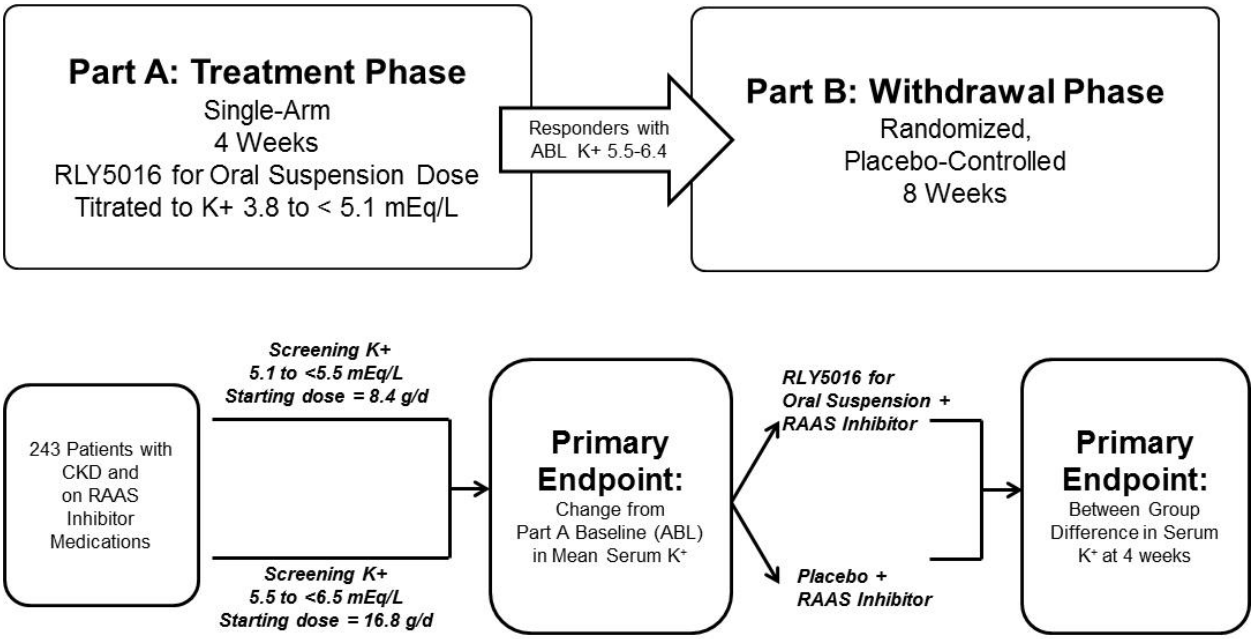
- Week 4, for subjects whose [K^+] remained in the range of 3.8 to < 5.5 mEq/L up to week 4; or
- An earlier time point for subjects with a [K^+] out of this range (i.e., < 3.8 or $\geq$ 5.5 mEq/L).

(Although Part B was 8 weeks long, the endpoint was the Week 4 value (or earlier value, as noted above.)

Secondary endpoints also assessed effects on serum potassium.

An overview of the trial is provided in Figure 2.

Figure 2: Overview of Study 301 (from page 29 of applicant's Clinical Overview [2.5])



Statistical Considerations: As prospectively agreed with FDA, the decrease in [K^+] from Part A Baseline to Part A Week 4 must have been $\geq$ 0.7 mEq/L with $p < 0.05$ for the 1° efficacy results to be considered positive (See Dr. Thompson's review for additional information).

The analysis population for efficacy endpoints in Part A was subjects who received one or more doses of patiromer. The analysis population in Part B was subjects who met eligibility criteria for Part B and were randomized.

The 1° endpoint in Part A was tested using a longitudinal repeated measures model that included binary covariates for baseline heart failure (yes/no) and type 2 diabetes (yes/no), as well as baseline [K^+] as a continuous covariate. The *p*-value was determined from a test comparing the mean change in [K^+] at Part A Week 4 to zero.

For Part B, changes from baseline [K^+] were ranked, and the treatment groups were compared using an ANOVA model with strata used at randomization. Part A baseline [K^+] <5.8 or $\geq$ 5.8 mEq/L and presence of Type 2 diabetes (yes/no) were included as covariates in the model, as well as a treatment indicator.

Study Results

Disposition

A total of 395 subjects were screened, of whom 243 (62%) were enrolled in Part A. All randomized subjects received at least one dose of patiromer, and 219 (90%) completed Part A. The most common reason for not completing Part A was an adverse event, and this occurred in 4% of subjects. Of the 107 subjects randomized in Part B, 82% of subjects randomized to patiromer completed Part B, compared to 58% of subjects randomized to placebo. The most common reason for not completing Part B in the placebo arm was meeting protocol-specified

withdrawal criteria for a high [K^+]. Otherwise, reasons for discontinuation were similar in the two treatment groups.

Demographics and Baseline Characteristics

In Part A, 64% of subjects were enrolled at sites in Eastern Europe (Georgia [12 sites], Ukraine [9 sites] and Serbia [3 sites]); 27% were enrolled at sites in the EU (Hungary [8 sites], Croatia [5 sites], Denmark [4 sites], Slovenia [2 sites], Italy [1 site] and the Czech Republic [1site]); and 9% were enrolled at 14 sites in the US. The number of subjects enrolled at each site ranged from 1 to 13.

In Part A, the median age was 65 years, 58% of subjects were male and 98% were Caucasian. Approximately 97% had hypertension, 57% had type 2 diabetes, 42% had heart failure, 25% had a prior myocardial infarction, and 45% had stage 4 or higher CKD. With respect to concomitant medication use, 70% of subjects in Part A were on an ACE inhibitor, 38% were on an ARB, 9% were on an aldosterone antagonist, 17% were on dual RAAS blockade and 54% were taking a non-RAAS inhibitor diuretic (thiazide or high ceiling diuretic).

The demographic characteristics, baseline co-morbidities, and baseline medication use of subjects in Part B were similar to those of subjects in Part A, although enrollment in Part B tended to be more 'Eastern European:' 79% of subjects were from sites in Eastern Europe, ~17% were from sites in the EU, and only 4% were from US sites.

Primary Endpoint

Part A:

There were 6 subjects (2.5%) in Part A who lacked even a single post-baseline [K^+] because of early withdrawal. These 6 subjects were not included in the 1° efficacy analysis, leaving 237 subjects in the analysis.

The trial met the prospectively specified 1° endpoint in Part A (Table 4). The overall mean (SE) change in [K^+] from Baseline to Week 4 was -1.01 (0.03) mEq/L (95% confidence interval [CI]: -1.07, -0.95, p<0.01). This change exceeded the threshold that had been set to address the potential impact of hemolysis (i.e., 0.7 mEq/L).

Table 4: Study 301: 1° Efficacy Endpoint: Change in [K^+], Part A (Source: Dr. Thompson's CDTL review; adapted from Dr. Kong's Table 3.5)

	Baseline Potassium Stratum		**Overall Population (n=237)**
	5.1 to < 5.5 mEq/L (n=90)	**5.5 to < 6.5 mEq/L (n=147)**	
	Serum Potassium (mEq/L)		
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 change from baseline, mean ± SE (95% CI)	-0.65 ± 0.05 (-0.74, -0.55)	-1.23 ± 0.04 (-1.31, -1.16)	-1.01 ± 0.03 (-1.07, -0.95)
***p*-value**			< 0.001

The prospectively planned 2° endpoint in Part A was the proportion of subjects with a centrally measured serum potassium level that was in the Part A target range (3.8 to < 5.1 mEq/L) at the Part A Week 4 visit. According to the Clinical Review, the proportion of subjects with a serum potassium level in this range at Week 4 was 76% (95% CI: 70%, 81%); the proportion was similar in the group with a baseline $[K^+]$ = 5.1 to < 5.5 mEq/L and in the group with a baseline $[K^+]$ = 5.5 to < 6.5 mEq/L.

Part B:

For Part B, the distributions of $[K^+]$ at baseline were similar in the placebo and patiromer groups. Part B also met its prospectively planned 1° endpoint, as shown in Table 5. The estimated between-group difference in the median change from the Part B baseline (placebo minus patiromer) was 0.72 mEq/L; 95% CI: 0.46, 0.99; *p* <0.01.

Table 5: Study 301: Change in $[K^+]$ from Part B Baseline to Part B Week 4 or the First Local Laboratory $[K^+]$ Result < 3.8 mEq/L or ≥ 5.5 mEq/L (Source: Statistical Review [Table 3.6] and Clinical Review [Table 17])

	Placebo n=52	**Patiromer n=55**
Baseline, mean (SD)	4.45 (0.34)	4.49 (0.43)*
Estimated median change in $[K^+]$ (quartiles)	0.72 (0.22,1.22)	0 (-0.3, 0.30)
Difference in median change Estimate (95% CI)	0.72 (0.46, 0.99)	
***p*-value**	<0.001	

*n = 54.

Dr, Kong, the statistical reviewer, confirmed the efficacy results for both Parts A and B using the data provided by the applicant. The reviewer also used other nonparametric statistical methods, such as the Wilcoxon test, to verify the primary efficacy results in Part B. The reviewer noted that there were few missing data in the study, and various methods of handling missing data would not importantly affect the 1° efficacy results.

Secondary Endpoints

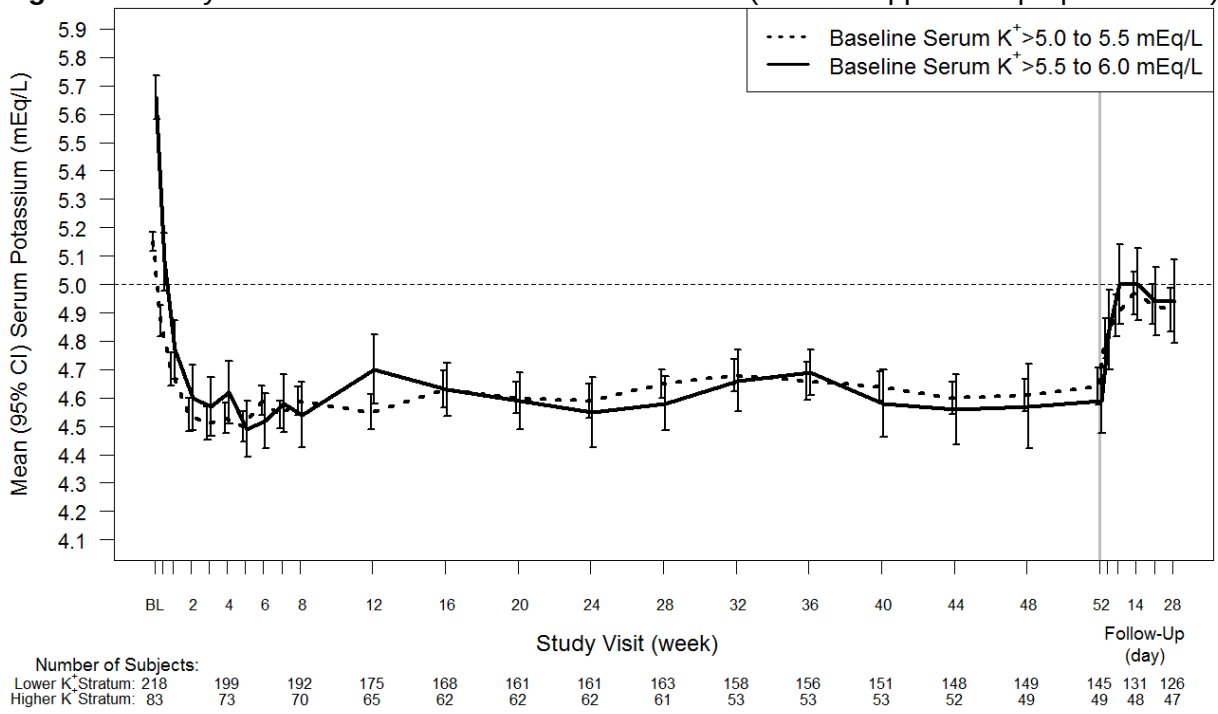
The prospectively planned 2° endpoints for Part B were: 1) the fraction of subjects with $[K^+] \geq$ 5.5 mEq/L at any time (post-Part B Baseline) through the Part B Week 8 visit; and 2) the proportion of subjects with $[K^+] \geq 5.1$ at any time (post-Part B Baseline) through the Part B Week 8 visit. As shown in Table 6, a greater proportion of subjects in the placebo arm, as compared to the patiromer arm, had $[K^+]$ values exceeding these thresholds.

Table 6: Study 301: 2° Endpoints in Part B: Proportion of Subjects with [K^+] above the Specified Value at Any Time (Post-Part B Baseline) through the Part B Week 8 Visit (Source: Statistical Review, Table 3.7)

2° Endpoint	Stratified Percentage (95% CI)			*p*-value
	Placebo n=52	Patiromer n=55	Difference	
Serum $K^+ \geq 5.5$	60 (47, 74)	15 (6, 24)	45 (29, 61)	<0.001
Serum $K^+ \geq 5.1$	91 (83, 99)	43 (30, 56)	48 (33, 63)	<0.001

Persistence of Efficacy
Study RLY5016-205 ("Study 205"), a phase 2 dose-ranging study with a long-term open-label treatment phase, provided support for persistence of efficacy. Subjects with Type-2 diabetes, CKD (eGFR 15 to <60 mL/min/1.73m^2), and hyperkalemia while on a RAAS inhibitor were treated for up to 52 weeks with patiromer. As shown in Figure 3, the reduction in [K^+] achieved in the days to weeks following initiation of therapy was maintained during the treatment period. Upon discontinuation of patiromer at Week 52, mean [K^+] increased, although it did not reach the pretreatment level.

Figure 3: Study 205: Potassium concentration over time (Source: Applicant's proposed label)



8. Safety

Exposure

According to Dr. Xiao's review, 734 subjects received at least one dose of patiromer in the clinical trials. Studies 205 and 301, described above, included 547 patients with hyperkalemia. Studies 202 and 204 included an additional 119 subjects without hyperkalemia but who were at risk for hyperkalemia (i.e., CKD and/or heart failure). All 4 of these studies enrolled patients

with underlying CKD and/or heart failure and evaluated dosing regimens relevant to labeling. Thus, the 666 patients from these 4 studies constitute the relevant population for the safety analyses.

A total of 219 subjects were treated for at least 6 months, and 149 were treated for at least 1 year. Although this exposure falls somewhat short of that recommended in ICH E1 Guidelines for chronic treatment of a non-life-threatening disease, FDA had noted that the nature and size of the safety database needed to support approval would depend upon whether the product was systemically absorbed. Given that patiromer was found not to be absorbed, the exposure was deemed to be adequate by all on the review team.

It is also important to point out that the controlled safety data base is limited; safety analyses are generally based on uncontrolled data. Strictly speaking, the randomized withdrawal phase of Study 301 provides controlled safety data; however, as Dr. Thompson notes, because patients who entered the randomized withdrawal phase had been previously treated with patiromer (and tolerated the drug), these data are difficult to interpret.

Subjects' mean age was 66. They were 60% male and 99% Caucasian.

Dr. Xiao focused on potential risks in light of the drug's mechanism of action, CMC and preclinical data, and experience with sodium polystyrene sulfonate, a similar drug. These potential risks include adverse GI effects, hypokalemia, non-specific binding to other cations, and systemic absorption of fluoride and calcium.

As many have pointed out, patiromer's most significant liability appears to be its potential to bind and interact with other oral medications, but the safety data base could not be used to explore this issue. I would add that extraordinarily large outcome studies would be required to probe for potential ramifications of drug-drug interactions causing loss of efficacy of particular drugs. (This is not feasible, although we recognize that small- or modest-sized pharmacokinetic studies could be designed to assess the potential for decreased exposure of concomitant drugs.)

Deaths: As discussed in Dr. Xiao's review, an independent Safety Review Board adjudicated all deaths and provided a determination of the relationship of each death to hyperkalemia and hypokalemia. The Board assessed 19 deaths as unlikely related to hypo- or hyperkalemia. The relationship between the serum potassium concentration and death could not be evaluated in one subject because serum potassium values were not available in a relevant timeframe before death.

Dr. Xiao concluded that most of the deaths were related to cardiac disorders. He noted that, given the lack of systemic absorption of the drug, there is no compelling reason to believe the deaths were causally related. He also found no deaths where hyperkalemia or hypokalemia seemed likely to be causal, although he noted that electrolyte concentrations were not always available in a reasonable timeframe prior to death.

Discontinuation for adverse events: Discontinuations for adverse events were not a major issue. According to Dr. Xiao's review, adverse events leading to permanent treatment discontinuation were reported in approximately 7% of subjects in the pooled safety data set, 5% of subjects in Part A of Study 301, and 9% of subjects in Study 205.

Serious adverse events: Dr. Xiao noted that there is no way to attribute causality of the 79 serious adverse events (reported in 8% of subjects) to patiromer. The serious adverse events appear typical for the patient population. There are no serious adverse events with preferred terms for specific electrolyte abnormalities, and none appear to be related to electrolyte abnormalities (though it is difficult to know this with certainty). Also, as noted by Dr. Xiao, there are no serious adverse events attributable to constipation, bowel obstruction, or diarrhea. Finally, there is no control group, and I would add that the numbers of serious adverse events in particular related categories are, in all cases, small.

Summary of specific adverse events of particular interest:

GI effects: There were no cases of severe GI toxicity plausibly related to patiromer. (There were 2 serious adverse events – both related to gastric ulcer.) Approximately 2% of subjects discontinued patiromer because of GI side effects. Constipation and diarrhea were among the most common adverse reactions, reported in 7.2% and 4.8% of subjects treated with patiromer, respectively. GI adverse events were typically reported within the first 4 weeks of treatment. Nausea, flatulence, and vomiting were each reported in ~2% of subjects. In Study 202, the study that provides the only placebo-controlled experience, the overall incidence of GI adverse events was higher in the patiromer group than in the placebo group (21 vs. 6%, respectively), supporting causality.

Hypokalemia: Analyses of adverse event and laboratory data were reassuring in terms of hypokalemia. As previously noted, $[K^+]$ was monitored in the phase 2 and 3 trials, and the dose of patiromer was titrated based on $[K^+]$ results.

As Drs. Xiao and Thompson point out, hypokalemia did not appear to play a role in any of the deaths and no subject had a serious adverse event of hypokalemia. Treatment discontinuations because of hypokalemia also were uncommon. According to Dr. Xiao's review $<$ 1% of subjects discontinued from studies because of hypokalemia and $<$ 2% of subjects were withdrawn for protocol-specified withdrawal criteria.

In total, ~ 4.7% of subjects (n=31) in the pooled safety set had a reported $[K^+]$ value < 3.5 mEq/L. The percentage of subjects was somewhat higher in the phase 2 trial (5.9%; n=18) and somewhat lower in the phase 3 trial (3.2%; n=8). Less than 1% of subjects (n=3, all from Study 205) had a $[K^+]$ of 3.0 mEq/L and no subject had a treatment emergent, on-study $[K^+]$ < 3.0 mEq/L.

Hypomagnesemia: Serum magnesium concentrations were assessed at screening and/or at baseline in Studies 301 and 205. Patients with a serum magnesium < 1.4 mg/dL at screening were excluded from Study 301. Study 205, in contrast, did not have an exclusion criterion for hypomagnesemia at baseline.

Adverse events of hypomagnesemia were not uncommon. According to the review team, in Study 205, adverse events of hypomagnesemia were reported in both the treatment initiation period (3% of subjects) and the long-term maintenance period (7.3% of subjects). In my own review of the applicant's ADAE.xpt data file, I found 30 (of 304) subjects in Study 205 with a preferred term of 'hypomagnesaemia' or 'blood magnesium decreased,' corresponding to ~10% of subjects. None of these adverse events was reported as serious.

The laboratory data show that 12 subjects (1.9% of total) had a magnesium value < 1.2 mg/dL post-baseline after a normal (or high) value at baseline. Virtually all of these subjects were in Study 205 (the longer of the two studies). No subject had a reported magnesium value < 1.0 mg/dL.

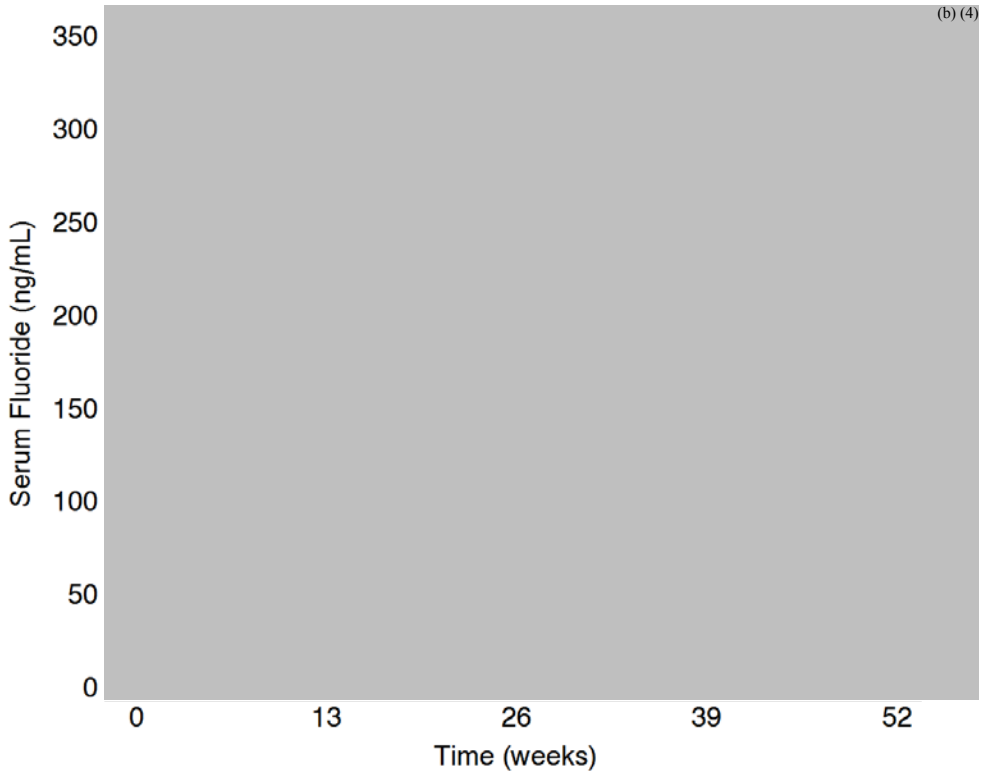
Hypomagnesemia did not appear to play a role in any of the sudden cardiac deaths, and no subject permanently discontinued treatment with patiromer because of hypomagnesemia.

Fluoride: In Study 205, [F^-] was assessed at baseline, Weeks 4, 8, 24, and 52 or end-of-treatment. In Part A of the Study 301, [F^-] was measured at screening and Week 4 or end-of-treatment; in Part B, [F^-] was measured at Weeks and Week 8 or end-of-treatment.

There were small changes in mean [F^-]; however, the changes were dwarfed by the standard deviations.

In my inspection of the [F^-] laboratory data, many of the values > (b) (4) appeared to be spurious in nature. In the patiromer development program, there were 54 subjects who had a reported [F^-] value > (b) (4). These patients are depicted in In Figure 4, where each line represents one patient (the software allowed the display of only 40 of 54 subjects). The numerous vertical trajectories (see left side of figure) represent what appear to be spuriously high values.

Figure 4: Serum Fluoride vs. Time for 40 of 54 Subjects with Reported Fluoride Values > (b) (4) (b) (4)



Hypercalcemia: Patiromer has the potential to increase calcium absorption, because calcium ions are exchanged for potassium ions. As discussed on pages 79-81 of Dr. Xiao's clinical review, analyses of laboratory and adverse event data did not suggest that patiromer causes a clinically relevant effect on serum calcium levels.

9. Advisory Committee Meeting

We chose not to convene the Cardiovascular and Renal Drugs Advisory Committee to evaluate this NDA. Although patiromer is a new molecular entity, its mechanism of action is similar to a product that has been marketed for decades (SPS). Moreover, the principal evidence of efficacy was a conventionally-designed study with an endpoint of serum potassium concentration, unquestionably the endpoint of interest here. The study was well executed; the effect size and the statistical persuasiveness were clear.

As noted by Dr. Thompson, the drug's potential to bind concomitantly administered oral medications represents a significant and unusual safety concern, but we felt that we possessed the internal expertise to consider and address this issue. A Regulatory Briefing was held to discuss the strategy used to evaluate patiromer's potential for drug-drug interactions, and to consider appropriate measures to mitigate risk. Our decisions reflect some of that discussion.

We believe our decision not to hold an advisory committee meeting to review this application was reasonable and appropriate.

10. Pediatrics

Dr. Thompson has provided an overview of the issues with respect to the pediatric study plan, and I refer you to her review and summary.

The pediatric studies will be deferred, because the drug is ready for approval in adults, and pediatric studies should be delayed until additional data are collected. Given its mechanism of action, patiromer is expected to be effective in pediatric patients; therefore, extrapolation of efficacy is acceptable; however, safety, tolerability, and dosing data are needed to guide the use of patiromer in the pediatric population.

The pediatric study plan is for two studies to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer in pediatric patients with hyperkalemia: one in children 2 to 18 years of age and another in children 0 to < 2 years of age. The review team believes that the two proposed studies are reasonable and will provide the data needed to assess safety and tolerability and support dosing and administration in pediatric patients with hyperkalemia.

The Pediatric Review Committee voiced concerns with respect to the potential for toxicity of xanthan gum present in the pediatric population, and suggested the Division seek additional information from the applicant regarding this safety concern.

There was also concern about the potential for hypercalcemia, especially in exclusively formula/breastfed infants. The Pediatric Review Committee recommended incorporation of safety monitoring to monitor for hypercalcemia. There were also concerns regarding potential

side effects from sorbitol and fluoride, and the Committee recommended careful monitoring, which will have to be addressed when the protocols are submitted.

11. Other Relevant Regulatory Issues

DSI Audits:

Three foreign clinical investigator site inspections and an applicant inspection were conducted. According to Dr. Gershon's review, no regulatory violations were observed during the applicant inspection or during inspections at the clinical investigator sites. All were classified as NAI.

Financial Disclosures:

As noted by Dr. Thompson and others, the applicant has adequately disclosed financial arrangements with clinical investigators, and there are no concerns about the integrity of the data.

Name Review:

The Office of Medication Error Prevention and Risk Management concluded that the proposed proprietary name, Veltassa, is acceptable.

12. Labeling

Some of the major labeling issues are described below:

Boxed Warning:

The Boxed Warning will note that patiromer binds to many other orally administered medications, which could decrease their absorption and reduce their effectiveness. It will advise separation of administration of patiromer and other oral medications by $\geq$ 6 hours.

1 INDICATIONS AND USAGE

Patiromer will be indicated for the treatment of hyperkalemia, and be silent with respect to duration of treatment. As noted above, given the time required for patiromer to travel to its site of action in the colon and reduce [K+], the label will include a critical Limitation of Use statement: "Veltassa should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action."

2 DOSAGE AND ADMINISTRATION

There will be advice to monitor serum potassium, and adjust the dose accordingly, waiting at least a week between upward adjustments.

There will also be a Medication Guide, to communicate, directly to patients, the importance of separating administration of patiromer and concomitant medications by $\geq$ 6 hours.

13. Decision/Action

The applicant's clinical development program demonstrated that patiromer is effective in decreasing serum potassium concentrations in patients with hyperkalemia. The clinical meaningfulness of serum potassium for this condition is clear.

In Study 301, Part A, the overall mean (SE) decrease in serum potassium, from Baseline to Week 4, was 1.01 (0.03) mEq/L, 95% CI: (1.07, 0.95), $p < 0.01$, a change that exceeded the threshold set to address the potential impact of hemolysis (0.7 mEq/L).

In the randomized withdrawal phase of Study 301 (Part B), the estimated between-group difference was 0.72 mEq/L, a finding that was also statistically persuasive ($p < 0.01$). These results were supported by Study 205, a dose-ranging trial with a long-term maintenance phase.

The principal safety concern is patiromer's potential to bind concomitant medications, reducing their absorption. Of 28 drugs tested for binding *in vitro*, half showed potentially important binding.

There was much discussion among the review team on how best to reduce the potential for drug-drug interactions. The Clinical Pharmacology review team reached the conclusion that administering patiromer and other oral medications at least 6 hours apart will prevent important patiromer-drug binding that would reduce efficacy of concomitant drugs. Their conclusion is based on a number of factors, including gastric emptying time (as reported in the literature), the impact of food and other factors on gastric emptying, the fact that some patients may have delayed gastric emptying (e.g., patients with diabetes, CKD), and the time required for absorption of immediate- and extended-release products. In essence, they concluded that a 6-hour difference in time of administration will ensure that patiromer is physically separated from other drugs prior to their point of absorption.

All understand that a 6-hour separation window is not possible for oral medications administered more frequently than BID.

There was discussion whether specific advice should be given in labeling for drugs that were found not to bind to patiromer *in vitro*, as practitioners could administer such drugs without concern about loss of their effect. A list of such medications, 'cleared' by *in vitro* studies, could have been included in Section 7 of labeling.

I believe, however, that knowledge that particular drugs could be administered concurrently could lead to the false perception that many, or most, drugs could be administered concurrently without concern about loss of efficacy, and this is clearly not the case. Moreover, there is consensus among the review team that the message in labeling should be simple and easily remembered: a single strategy for all medications (i.e., separate by 6 hours).

Concomitant medications will be prescribed by many practitioners and dispensed by many pharmacies. In the end, it is the patient who bears the responsibility for separating administration of patiromer and other drugs; therefore, the message must be clear so that the directions are remembered and followed by patients. And because conveying this message to the patient is so important, patiromer will be dispensed with a Medication Guide.

One point that has not been considered by the review team is that not all medications with the potential to be bound by patiromer are important. For example, non-prescription drugs, and, for that matter, most drugs for symptom relief, can be administered at any time relative to patiromer, because for these drugs, loss of efficacy is not clinically important. Delivering this message to patients, however, without undermining the main message, would be difficult.

I agree with Dr. Thompson's view that a Boxed Warning is appropriate for patiromer. According to our guidance, a Boxed Warning is ordinarily used when there is a "serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug." In this case, patiromer-drug binding can lead to loss of important efficacy for a number of drugs, which could be prevented with appropriate use of the drug.

I also agree with Dr. Thompson with respect to discouraging long-term use. She notes that discouraging long-term use would mitigate the problem of drug-drug interactions by simply limiting the window of opportunity for interactions. But she points out the unmet need for therapies that can be used chronically to treat hyperkalemia – to maintain potassium in a normal or near-normal range in the face of drugs that lead to potassium retention, i.e., RAAS inhibitors.

The available data from Study 205 show persistence of effect out to 1 year, and the safety data, though somewhat limited in utility, go out to 1 year as well. Thus, I agree with Dr. Thompson, and believe the indication should reflect what the drug is for (treatment of hyperkalemia), and be silent about duration. Moreover, the indication statement for sodium polystyrene sulfonate, a product that shares some of patiromer's liabilities, does not limit the duration of use.

Beyond drug-drug interactions, the other safety concerns seem to be fairly well characterized. Adverse effects include hypokalemia, adverse GI reactions, hypomagnesemia, systemic absorption of its counter-ion (calcium), and possibly absorption of fluoride. Risks of hypokalemia and hypomagnesemia can be mitigated through monitoring. GI reactions are self-limited. The evidence for fluoride absorption is not strong.

Recommendation for Risk Evaluation and Management Strategies (REMS): No one on the review team has argued for the utility of a REMS.

Recommendation for other Postmarketing Requirements and Commitments: We have heard a range of opinions on whether postmarketing studies should be performed to address potential drug-drug interactions. Some have argued that clinical studies are needed to obtain *in vivo* data to determine the relevance of the *in vitro* findings – to evaluate whether 6-hour separation is appropriate (i.e., whether, on one hand, it is sufficient; and whether, on the other hand, the separation could be shortened).

In the end, the review team was convinced that a 6-hour separation between administration of patiromer and concomitant medications will be sufficient to avoid reduced efficacy of the latter.

I am convinced that developing a list of drugs that <u>could</u> be co-administered with patiromer, or administered less than 6 hours apart, would compromise the message with respect to drugs that <u>cannot</u> be administered within 6 hours. Again, we believe we need to keep the message simple with respect to spacing drugs. And because we are confident that 6 hours will be sufficient to prevent binding of concomitant drugs and avoid important diminution of their effects, there is no reason to require a study to test this hypothesis.

Post-marketing Agreements

The deferred pediatric studies, required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act, are required postmarketing studies:

Study 1: A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Veltassa for Oral Suspension in Children and Adolescents 2 to 18 Years of Age with Hyperkalemia

Study 2: A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Veltassa for Oral Suspension in Infants and Toddlers Under 2 Years of Age with Hyperkalemia

The time lines and specific expectations are delineated in the approval letter.

Benefit and Harm

Patiromer represents a new molecular entity for the treatment of hyperkalemia. Patiromer's effectiveness is established on the basis of 2 studies, where it was shown to decrease the serum potassium concentration by roughly 1 mEq/L.

Patiromer's actual benefit to patients is difficult to characterize. ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and, most recently, sacubitril plus valsartan, have been shown to decrease morbidity and/or mortality in patients with CKD and/or heart failure, but their use is limited by hyperkalemia in some patients. In essence, by helping to manage the hyperkalemia, patiromer could enable the use of these therapies in patients with CKD and heart failure.

Patiromer's risks are manageable, as noted above. Some of the side effects cause symptoms that would lead patients to seek medical attention or discontinue the drug (GI effects); others would be detected through routine monitoring (hypokalemia, hypomagnesemia). Aside from the potential for severe electrolyte abnormalities in patients who are not well monitored, we are not aware of any potential for irreversible harm. The label will urge appropriate patient monitoring.

The typical patient in the development program was a 66 year-old Caucasian from Eastern Europe. Given patiromer's mechanism of action, however, I find little reason to be concerned that racial or ethnic factors could influence either the drug's effects on potassium or its side effect profile. In short, I believe that the results of the studies can be reasonably extrapolated to a US patient population.

Having negotiated the labeling with the applicant, patiromer will be approved today with agreed upon labeling and the following indication statement:

> "Veltassa is indicated for the treatment of hyperkalemia."

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
10/21/2015