CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205739Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to Clinical Pharmacology

NDA:	205739
PRODUCT (Generic Name):	Patiromer (RLY5016)
PRODUCT (Brand Name):	Veltassa®
INDICATION:	Treatment of Hyperkalemia
DOSAGE FORM:	Powder for Oral Suspension
DOSAGE STRENGTHS:	8.4 g, 16.8 g and 25.2 g patiromer/packet
REVIEWER:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Rajanikanth Madabushi, Ph.D.
OCP DIVISION:	Division of Clinical Pharmacology I
OND DIVISION:	Division of Cardiovascular and Renal Products

1 SUMMARY

This document provides the basis for the recommendation to space administration of patiromer and other oral medications by 6 hours to avoid potential drug interactions.

2 BACKGROUND

Patiromer for oral suspension (NDA 205739, Veltassa®) is a non-absorbed, cation-exchange (b) (4) with a proposed indication for the treatment of hyperkalemia. The interaction potential of patiromer has been a significant review issue. Patiromer's potential to bind other oral medications, thus reducing their bioavailability and limiting their efficacy, was evaluated in *in vitro* studies. Of the 28 drugs that were tested, half showed a positive interaction (>30% binding) with patiromer. Based on an assessment of patiromer's physicochemical characteristics, interactions are expected with cationic, anionic (due to the calcium-sorbitol counterion) as well as neutral (hydrophilic interaction) oral drugs when concomitantly administered. Due to the number of interactions observed and concerns about potential interaction with un-tested drugs, a pragmatic approach that is simple and feasible is needed to address patiromer's drug-drug interaction (DDI) liability.

The applicant proposed an approach to separate the time of dosing of patiromer and other orally administered medications by (b) (4) hours based on gastric emptying concept. While utilizing the concept of gastric emptying to space drug administration seems to be scientifically justifiable, a (b) (4) hour separation window does not appear to be sufficient. Upon review of the available information, the review team concluded that a 6 hour separation seems appropriate. This was communicated to the applicant in a General Advice Letter issued on September 16, 2015 and is further discussed on Section 3.

3 KEY CONSIDERATIONS FOR DETERMINING THE DURATION OF SEPARATION

The following attributes are critical for deriving the separation time to mitigate the potential for drug interactions:

1) Factors affecting gastrointestinal (GI) motility
2) The time required for maximum (T_{max}) or near-maximal absorption of co-medications

Factors affecting GI motility:

GI motility can be described by GI transit time which includes gastric emptying time and intestinal and colonic (later part of the GI) transit times.

Gastric emptying time (GET) is defined as the elapsed time between the ingestion and emptying of the contents of the stomach caused by the relaxation of the pyloric sphincter into the intestine. Gastric emptying is relatively prolonged especially in the fed state as one of the functions of the stomach is to grind food into smaller particles and allow a regulated supply of calories into the small intestine. Gastric emptying time is variable and depends upon several factors such as the type of the meal (solid vs. liquid), size of the meal, frequency of meals, particle size, caloric value, posture, stress, etc. (Wilson 2011).

There are no dedicated studies of gastric emptying time of patiromer (particle size of (b) (4)). However, in general, gastric emptying for pellets with a particle size of 0.3 – 1.2 mm in subjects without gastrointestinal disorders is reported to be in the range of 0.5 – 4 hours (Davis, 1986). Delayed gastric emptying in various patient populations is well documented, especially in diabetic patients with gastroparesis. Following a standardized meal (255 kcal), the GET in gastroparetic patients (Median: 5.4 hours) was found to be 50% slower compared to healthy controls (Median: 3.6 hours). Similar results have been reported in other publications, with GETs 34% - 77% slower in diabetic patients compared to those in normal subjects (Javas, 2015 and Lartigue, 1994). Further, in chronic hemodialysis patients, the emptying time is reported to be 66% slower compared to normal subjects (Schoenmakere, 2001). However, there are no dedicated studies characterizing the GET of small particle and pellets in these patient populations with GI disorders. Based on these data, it is reasonable to expect the GET for patiromer in the target population to range from 2 – 6 hours. Hence a 6 hour separation between patiromer and other oral medications will ensure an adequate physical separation, thus mitigating the potential for a drug interaction.

Following gastric emptying, the transit to the small intestine and eventually to colon is expected to generally occur without any stoppage. The time elapsed from GET until the chyme arrives at the caecum is defined as small bowel transit time (SBTT). Literature reports indicate that SBTT (4 – 6 hours) is less dependent on the fasted or fed state (Davis, 1986 and Macheras, 2013). The SBTT is reported to be similar between healthy subjects and patients with gastroparesis

(Sarosiek, 2010). Hence a separation of 6 hours between patiromer and other oral medications based on the GET will ensure separation up to the caecum.

The time elapsed from the arrival of the chyme at ileocaecal junction until the exit from the body is defined as colonic transit time (CTT). The CTT is prolonged in gastroparetic patients (Median: 18 hours vs. 46 hours) compared to healthy controls (Sarosiek, 2010). However, this prolongation in the CTT is less of a concern with respect to interaction potential because drug absorption of most medications primarily occurs in the small intestine, with the stomach and colon having much reduced absorptive capacity for drugs (Wilson, 2011). The potential for interaction cannot be completely ruled out for products that are designed to release the drug in colon especially when the patiromer is administered prior to the other medication. Generally colonic targeted release is not a common approach for drug release. This approach is used for drugs that are intended to be released in colon and generally administered as suppositories or enemas, to improve patient compliance. Some of the FDA approved products are Delzicol® and Uceris®. However, it should be noted that colon is a K+ rich environment and K+ will compete with other drug released in colon for binding with patiromer. This lessens the concern for an interaction with such products.

The time required for maximum or near-maximal absorption of co-medications:

For Immediate–release (IR) products, T_{max} usually occurs within ~ 2 hours. For such products a shorter separation time of 2 - 3 hours can be considered especially if the other medication is administered prior to patiromer. But this separation may not be adequate if the patiromer is administered prior to the other medication and necessitates a 6-hour separation in dosing to account for the GET of patiromer.

For Extended-release (ER) products shorter separation times cannot be considered as the absorption is prolonged and the T_{max} generally occurs later. The release from the drug product and its absorption can occur throughout its transit in the small bowel. As mentioned previously, once gastric emptying occurs, the movement over the rest of the GI tract remains at approximately same rate. Hence, a 6-hour separation of dosing will result in patiromer and other extended release oral medications entering the small intestine at different times and would not be expected to come in contact in the small intestine. This will ensure no interference in the absorption of the drug from the ER formulation as it moves through the small intestine thus mitigating the potential for interaction.

4 CONCLUSIONS AND RECOMMENDATIONS

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

5 MATERIALS REVIEWED

1. Slide decks for CDER Regulatory Briefing on September 18, 2015
2. NDA 205739 General Advice Letter issued on September 16, 2015.
3. Wilson CG. The Organization of the Gut and the Oral Absorption of Drugs: Anatomical, Biological and Physiological Considerations in Oral Formulation Development, *Controlled Release in Oral Drug Delivery*, 2011.
4. Davis SS and et al. *Transit of Pharmaceutical Dosage Forms through the Small Intestine. Gut*, 27: 886-892, 1986.
5. Javas H and et al. Relation between clinical features and gastric emptying time in diabetic patients. *Nuclear Medicine Review,* 18, 1: 3–6, 2015.
6. Lartigue S and et al. Inter- and Intrasubject Variability of Solid and Liquid Gastric Emptying Parameters, A Scintigraphic Study in Healthy Subjects and Diabetic Patients. *Digestive Diseases and Sciences,* VoL 39, No. 1, 109-115, January 1994.
7. Schoenmakere GD and et al. Relationship between gastric emptying and clinical and biochemical factors in chronic haemodialysis patients *Nephrol Dial Transplant,* 16: 1850-1855, 2001.
8. Macheras P and et al. Keeping a critical eye on the science and regulation of oral drug absorption: A review. *Journal of Pharmaceutical Sciences,* Volume 102, No. 9: 3018 – 3036, 2013.
9. Sarosiek I and et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Alimentary Pharmacology & Therapeutics*, Volume 31, Issue 2, pages 313–322, January 2010.
10. Newton JM. Gastric Emptying of Multi-Particulate Dosage Forms. *Int. J. Pharmaceutics,* 395: 2-8, 2010.

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/s/

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10/16/2015

RAJANIKANTH MADABUSHI
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10/16/2015

Clinical Pharmacology Technical Document

PRODUCT (Generic Name):	Patiromer (RLY5016)
NDA:	205-739
PRODUCT (Brand Name):	Veltassa®
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DOSAGE STRENGTHS:	8.4 g, 16.8 g and 25.2 g patiromer/packet
INDICATION:	Treatment of Hyperkalemia
NDA TYPE:	NME
SUBMISSION DATE:	10/21/2014
SPONSOR:	Relypsa, Inc.
REVIEWERS:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Rajanikanth Madabushi, Ph.D. & Jeffry Florian, Ph.D.
OCP DIVISION:	DCP 1 and DPM
OND DIVISION:	DCRP

1. Summary of findings

This document provides the technical details for the key questions in the Clinical Pharmacology QBR:

- (QBR 2.2.3) Baseline serum potassium is the most predictive parameter of change in serum potassium.
- (QBR 2.2.3) A plateauing dose-response relationship was identified over patiromer doses from 8.4 g/day to 33.6 g/day. Incremental reductions in serum potassium from baseline were observed with increasing doses of patiromer, with the largest difference observed between 8.4 g/day and 33.6 g/day.
- (QBR 2.2.3) An initial dose of 8.4 g/day is appropriate for all patients with an option to titrate in 8.4 g/day increments. The interval between dose titrations should be at least 7 days to allow for maximum response.

The key questions were answered using a likelihood-based mixed model for repeated measures (MMRM). The MMRM model was developed by the Applicant using data from the integrated summary of efficacy data set, including data from a Phase II (RLY5016-205) and Phase III (RLY5016-301) study.

2. Documentation and assessment of Applicant's model

In response to the Starting Dose and Titration comments in the Mid-Cycle Communication (5/1/2015) the Applicant developed a MMRM model to characterize the dose-response relationship using SAS. This model was submitted to the Agency on 6/1/2015. The model was developed using data from a Phase II (RLY5016-205) and a Phase III (RLY5016-301) study.

2.1. Data

2.1.1. RLY5016-205

The Phase II study, RLY5016-205, is a multicenter, randomized open-label study with three cohorts. Cohorts 1 and 2 had a run-in period of up to 4 weeks in duration and cohort 3 had no run-in. Cohort 1 included all eligible non-hyperkalemia subjects (serum potassium 4.5 to 5.0 mEq/L), cohort 2 was deactivated (only had three subjects randomized to RLY5016). Cohort 3 included hyperkalemia subjects with serum potassium >5.0 to <6.0 mEq/L at

screening, who continued on their ACEI and/or ARB drugs and were randomized to treatment with RLY5016 without a run-in period (See Table 1). The study included a total of 306 subjects.

At each visit the patients were either: kept on the same dose, up titrated or down titrated based on their serum potassium, generally by changes of 8.4 g/day described in further detail in RLY5016-205 study report on pages 57-58.

Table 1. Number of subjects by stratum, cohort and randomized starting dose for RLY5016-205.

	RLY5016 for Oral Suspension Starting Dose (g/day patiromer)								
	Stratum 1 Local Laboratory Serum K^+ > 5.0 - 5.5 mEq/L				Stratum 2 Local Laboratory Serum K^+ > 5.5 - < 6.0 mEq/L				
Cohort[a]	8.4 g/day (N=74)	16.8 g/day (N=74)	25.2 g/day (N=74)	Overall (N=222)	16.8 g/day (N=26)	25.2 g/day (N=28)	33.6 g/day (N=30)	Overall (N=84)	Total (N=306)
Cohort 1	16	15	16	47	2	4	5	11	58
Cohort 2	1	1	1	3	0	0	0	0	3
Cohort 3	57	58[b]	57[b]	172	24	24	25	73	245
Overall	74	74	74	222	26	28	30	84	306

Source: RLY5016-205 study report page 98 – Table 10

2.1.2. RLY5016-301

The Phase III study RLY5016-301 is a multicenter, single-blind study of RLY5016 consisting of two parts. Part A was a 4-week assessment of RLY5016 oral suspension dosing for the treatment of hyperkalemia in patients with screening serum potassium of 5.1 to < 6.5 mEq/L. Eligible patients were assigned to either 8.4 g/day starting dose or 16.8 g/day starting dose based on screening serum potassium. Part B was a randomized, placebo-controlled 8-week assessment of the withdrawal of RLY5016.

Similar to patients in the Phase II trial RLY5016-205, there was a set of criteria used for dose up or down titration by 8.4 g/day to reach the target of 3.8 to < 5.1 mEq/L. The titration scheme is summarized in RLY5016-301 study report on page 73.

Table 2 Number of subjects by stratum, cohort and randomized starting dose for RLY5016-301.

Table 13 Enrollment by Region and Country (Part A ITT Population)

Region/Country	Dose Group 1 5.1 to < 5.5 mEq/L N = 92 n (%)	Dose Group 2 5.5 to < 6.5 mEq/L N = 151 n (%)	Total 5.1 to < 6.5 mEq/L N = 243 n (%)
Eastern Europe (non-EU)	**47 (51)**	**109 (72)**	**156 (64)**
Georgia	12 (13)	67 (44)	79 (33)
Ukraine	28 (30)	35 (23)	63 (26)
Serbia	7 (8)	7 (5)	14 (6)
European Union	**31 (34)**	**34 (23)**	**65 (27)**
Hungary	17 (18)	16 (11)	33 (14)
Croatia	5 (5)	5 (3)	10 (4)
Denmark	5 (5)	3 (2)	8 (3)
Italy	0	6 (4)	6 (2)
Slovenia	3 (3)	3 (2)	6 (2)
Czech Republic	1 (1)	1 (1)	2 (1)
United States	**14 (15)**	**8 (5)**	**22 (9)**
United States	14 (15)	8 (5)	22 (9)

Source: RLY5016-301 study report page 115 – Table 13

2.1.3. Integrated summary of efficacy
The model was built using data from the integrated summary of efficacy (ISE) full analysis data set (idose). This data set includes data from RLY5016-205 and part A of RLY5016-301. Only observations for doses of 8.4, 16.8, 25.2 and 33.6 g/day at visits day 3 and week 1 through 4 were included in the analysis, this resulted in approximately 2% of the data being excluded.

2.3. Methods

2.3.1 Model
The Applicant developed a MMRM model based on centrally measured serum potassium from the ISE data set (idose):

$$\begin{aligned} &reduction\ in\ serum\ potassium\ (PR) \\ &\quad = serum\ potassium\ at\ last\ visit\ (prek) + \ dose\ at\ last\ visit(adosetrt) \\ &\quad + time\ since\ last\ visit(tchg) + visit(avisit) + visit * dose\ at\ last\ visit(avisit * adosetrt) \\ &\quad + serum\ potassium\ at\ last\ visit * visit(prek * avisit) \end{aligned}$$

where the variable names in the ISE data set is given in parenthesis and there is a repeated term on 'avisit' by subject id (subjid) grouped by dose at last visit (adosetrt).

The model was fit using PROC MIXED in SAS 9.4:

(b) (4)

2.3.2 Model diagnostics and statistical analysis
Appropriateness of model fit is assessed by evaluation of the log likelihood of the model as well as model diagnostic plots of:

- Relationship between predicted reduction in serum potassium and residual error
- Relationship between residual error and model terms

Afterwards, the model is used to compute the least-squares estimates by dose to evaluate the dose response relationship.

2.4. Results

2.4.1. Model diagnostics
The model fit the data reasonably well as observed by the log likelihood ratio (loglik= (b) (4)) and no relationship was observed between predicted reduction in serum potassium and residual error (Figure 1). In addition, no relationship was observed between model parameters and residual error (Figure 2).

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Figure 1 Predicted reduction in serum potassium (x-axis) versus residual (y-axis). The line range represents the data distribution (5%, 50% and 95%).

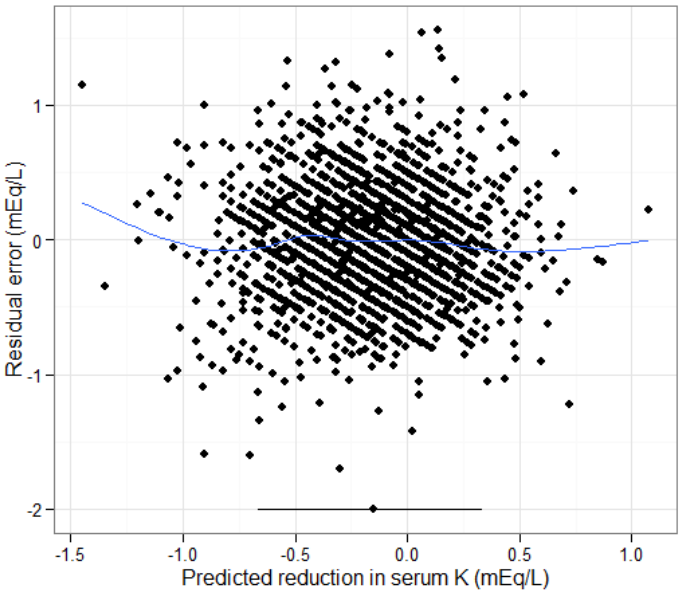
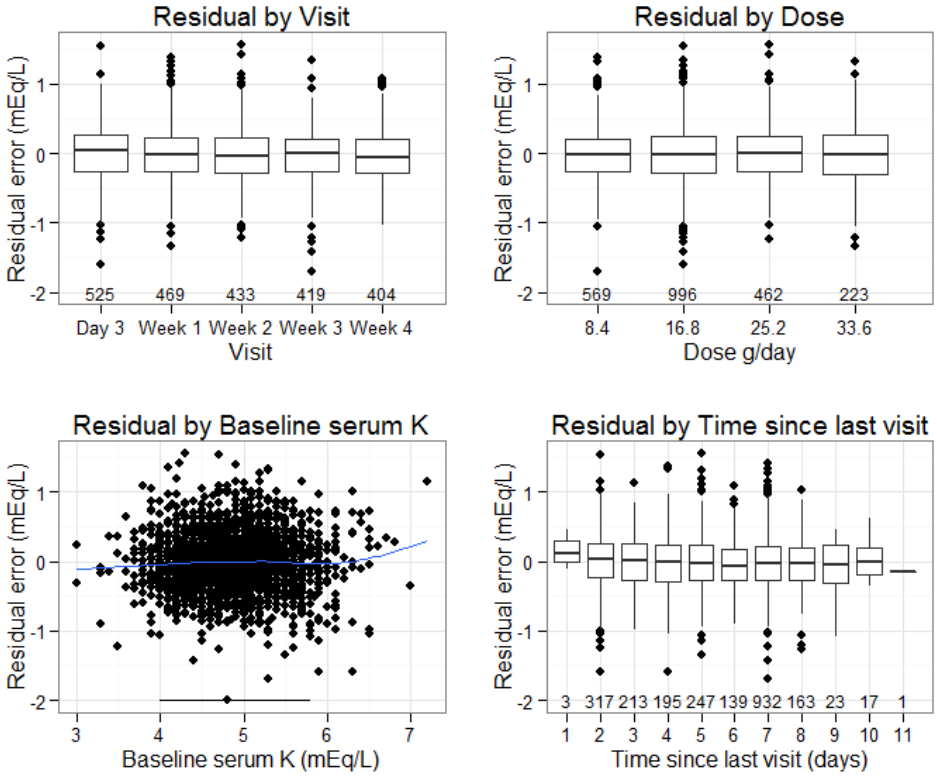


Figure 2 Model terms (avisit, dose, baseline serum potassium, time since last visit) on the x-axis versus residual error (y-axis). The number below each group (e.g., visit, dose, time since last dose) reflects the number of measurements for that group. The line range and point in the residual by baseline serum K reflect median and lower 5% to 95% of the data.



2.4.2 Assessment of model parameters and least-squares estimates

Using the model the parameter estimates for all the significant parameters were obtained (Table 3). The parameters are similar to the analysis provided by the Applicant (Response to Mid-Cycle Communication, 5/1/2015) and suggest that the most influential parameter for describing the change in serum potassium is baseline serum potassium at that visit (Response to Mid-Cycle Communication, Table 3, page 9).

Table 3. Parameter estimates from Applicant's model for parameters with p<0.05

Parameter	Estimate (Standard Error)	P-value
Intercept (mEq/L)	3.15 (0.23)	<0.001
pre_k (mEq/L)	-0.66 (0.04)	<0.001
avisit – Week 3	-1.17 (0.31)	<0.001
pre_k * avisit – Week 3 (mEq/L)	0.22 (0.06)	<0.001
adose_trt (25.2 g/day) * avisit – Week 3	0.18 (0.09)	0.045

Using the model the least-squares estimates of the effect by dose was computed (Table 4). From these results a statistical significant difference between the lower dose groups (8.4 g/day and 16.8 g/day) and the higher dose groups (25.2 g/day and 33.6 g/day) can be observed.

Table 4. Least-squares mean of the reduction in serum potassium at week 4 and difference between dose groups 8.4 g/day and 16.8 g/day.

	8.4 g/day	16.8 g/day	25.2 g/day	33.6 g/day
LS means (SEM)	-0.11 (0.02)	-0.15 (0.02)	-0.18 (0.2)	-0.22
95% CI	-0.15, -0.08	-0.18, -0.11	-0.22, -0.15	-0.28, -0.16
p-value for testing LS mean = 0	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
8.4 g/day vs				
Difference of LS means (SEM)		0.03 (0.02)	0.07 (0.03)	0.10 (0.04)
95% CI		-0.01, 0.08	0.02, 0.12	0.03, 0.17
p-value for testing difference		0.18	**0.0074**	**0.0044**
16 g/day vs				
Difference of LS means (SEM)			0.04 (0.02)	0.07 (0.03)
95 % CI			0.00, 0.09	0.00, 0.14
p-value for testing difference			0.10	**0.0355**

3. Reviewer's analysis[1]

The reviewer performed additional sensitivity analyses on the Applicant's model to assess the robustness of the model. In addition, the reviewer used the Applicant's model to project changes in serum potassium for hypokalemic

[1] These additional analyses were independently conducted by the reviewer.

patients for various scenarios to answer the previously described key questions in the Clinical Pharmacology QBR regarding starting dose and dose titration interval.

3.1. Methods

3.1.1. Model sensitivity analysis

The model sensitivity analysis focused on data excluded by the Applicant from the initial analysis and the inclusion of a grouped repeated statement in the model initially proposed by the Applicant. It was unclear to the reviewer what the rationale of the grouped term on the repeated measures statement, as the grouping was on dose since last visit (adose_trt), which can change between visits.

To evaluate the sensitivity in the model to the grouping term and data exclusion (~2% data were excluded), the reviewer conducted a comparison in the least-squares estimates. In addition, the reviewer will explore using dose as a continuous covariate.

3.1.2. Predictions of drug-effects with fixed dosing regime

Two fixed dose scenarios were simulated to evaluate the impact of various starting doses and to assess an appropriate time interval for dose titration: i) dose fixed to the initial value in the respective studies; or ii) dose fixed to 8.4 g/day in all patients. The predicted average reduction in serum potassium was computed iteratively using the fixed effects from the model developed by the Applicant, in the following manner using R 3.1.2 (provided in Appendix 1. R code for prediction of drug-effects with fixed-dosing):

1. Predict average reduction in serum potassium for day 3 (first visit)
2. Use predicted reduction for day 3 visit and baseline for day 3 visit to compute baseline for week 1 visit
3. Predict average reduction in serum potassium for week 1 (second visit)
4. Repeat steps 1) through 3) for all remaining visits

The predictions as described above are carried out using patient serum potassium at the baseline visit and dose and subsequently averaged by visit.

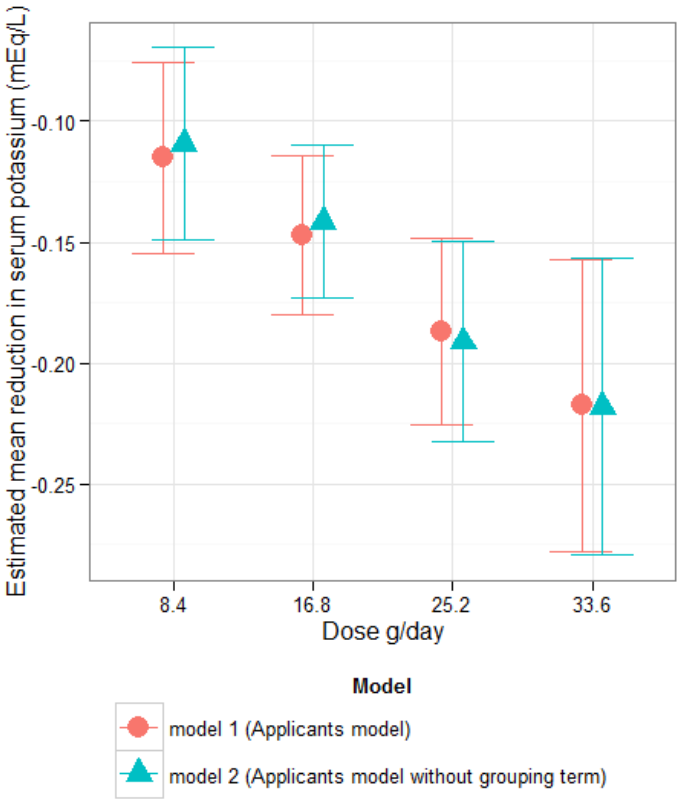
3.2. Results

3.2.1. Model sensitivity analysis

Comparison of the least-squares means using the model as proposed by the Applicant (model 1) and a revised model without the grouping term on the repeated effect (model 2) is shown in Figure 3 below.. In addition, the AIC for the two models were computed:

- Model 1 – Applicant's model as described in Section 2.3. Methods. (AIC = 2381.7)
- Model 2 – Grouping on repeated effect removed (AIC = 2376.8)

Figure 3 Residual error (left panel) and predicted reductions in serum potassium (right panel) for four different models: model 1 (Applicant's model, red circles) and model 2 (repeated measures grouping removed from Applicant's model, blue triangles)



The model least-squares estimates for with either model are comparable, but the model without the grouped term has a slightly lower AIC (model 2: 2376.8 vs. model 1: 2381.7). Based on this the reviewer views the model without the grouped term as more appropriate compared to the original model even though the differences are negligible. Further simulations are conducted Applicant's model. In addition, a model with dose as continuous dose was evaluated, which produced comparable least-squares estimates to model 1 and model 2. Lastly, the reviewer explored inclusion of all data (57 measurements or approximately 2% of the overall dataset); however, inclusion of this data, but this resulted in model convergence issues hence the final model excluded these measurements.

3.2.2. Prediction of drug-effects with fixed dosing

Figures with results of the predicted time-course by three patient groups (i) all patients; ii) patients considered as 'not-titrated' where starting and ending dose were the same; and iii) 'titrated' patients where starting and ending dose differed) by starting dose for either the fixed dose scenario or dose fixed to 8.4 g/day. The summarized results by the week 4 visit is shown below in Figure 4, more detailed time-course is shown in Figure 5 (initial dose) and Figure 6 (dose fixed to 8.4 g/day).

From the figures it can be seen that the serum potassium reductions were higher in the dose groups that started at a higher patiromer daily dose, though this greater change was because the patients in the higher dose groups also had higher baseline serum potassium (e.g., the most predictive parameter for decrease in serum potassium). Moreover, the simulations show that the maximum response on a fixed dose is reached sometime between week 1 and 2, after which all the time profiles flatten out from week 2 to week 4. This result suggests that the full effect of a dose change (or initial dosing) will not be realized until between weeks 1 to 2.

The predicted change from baseline in serum potassium is higher on average compared to the observed data for not titrated patients, while an opposite trend (i.e., under prediction) was predicted for patients that were titrated. This is counterintuitive, as the patients that were titrated are expected to have a lower serum potassium than if they had not been titrated (the projected line). One possible explanation for this is that the model does not include a random term,

and the projections are thus population-based projections. So, when comparing population-based projections to patients that were titrated, and who are more likely to be poor responders, the projections will likely overestimate their response.

As expected the projected mean serum potassium if the dose was fixed to 8.4 g/day in all patients (Figure 4) is higher than if the dose is fixed to the initial patient dose (Figure 5), and the difference is larger for the patients in the 25.2 g/day and 33.6 g/day initial dosing groups. These observations are consistent with the results from the Applicant showing that the dose difference was not significant before comparing 25.2/33.6 g/day and 8.4 g/day. Of note, the model predicts that even with a dose of 8.4 g/day that it may be possible for many patients, including those patients with higher baseline serum potassium levels to achieve normalization of serum potassium levels over a period of 4 weeks (Figure 6).

Figure 4. First panel shows the data for all patients, the second panel for patients who did not need dose tit0ration and the third panel is for patients that underwent dose titration according to the titration scheme in the included studies. In each panel observed data are the red diamonds at week 4, the green triangles are predicted serum potassium at week 4 without dose titration and the blue squares are predicted serum potassium at week 4 corresponding to fixed daily dose to 8.4 g/day.

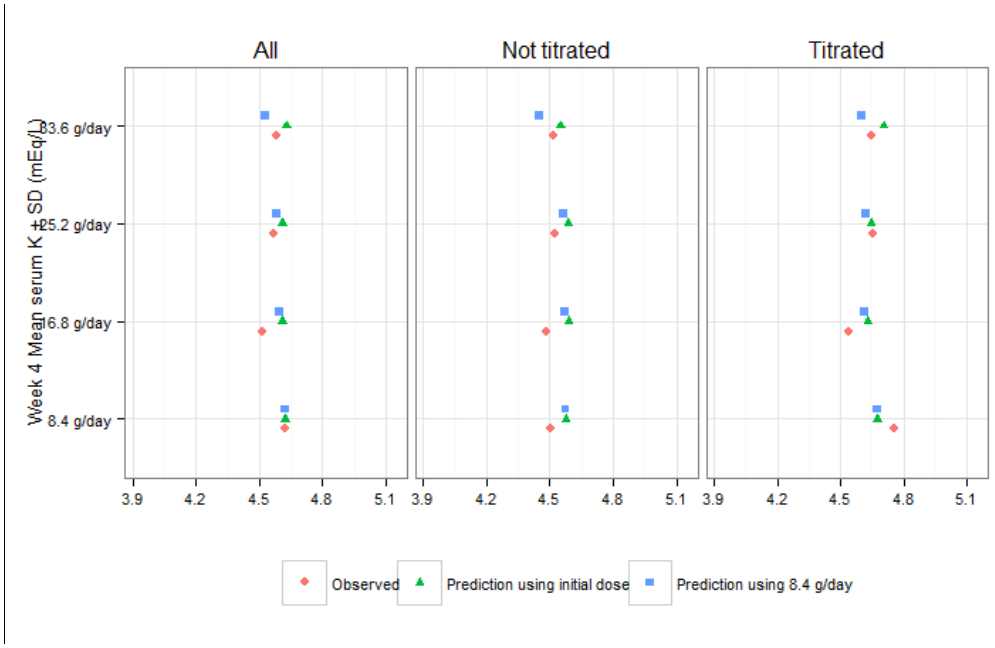


Figure 5 Fixed dosing simulations (no up titration) based on the prediction methodology described, for either all patients (first column) by starting dose, patients starting and ending on the same dose (not titrated, middle column) by starting dose or patients that were titrated (not starting and ending on same dose) by initial dose.

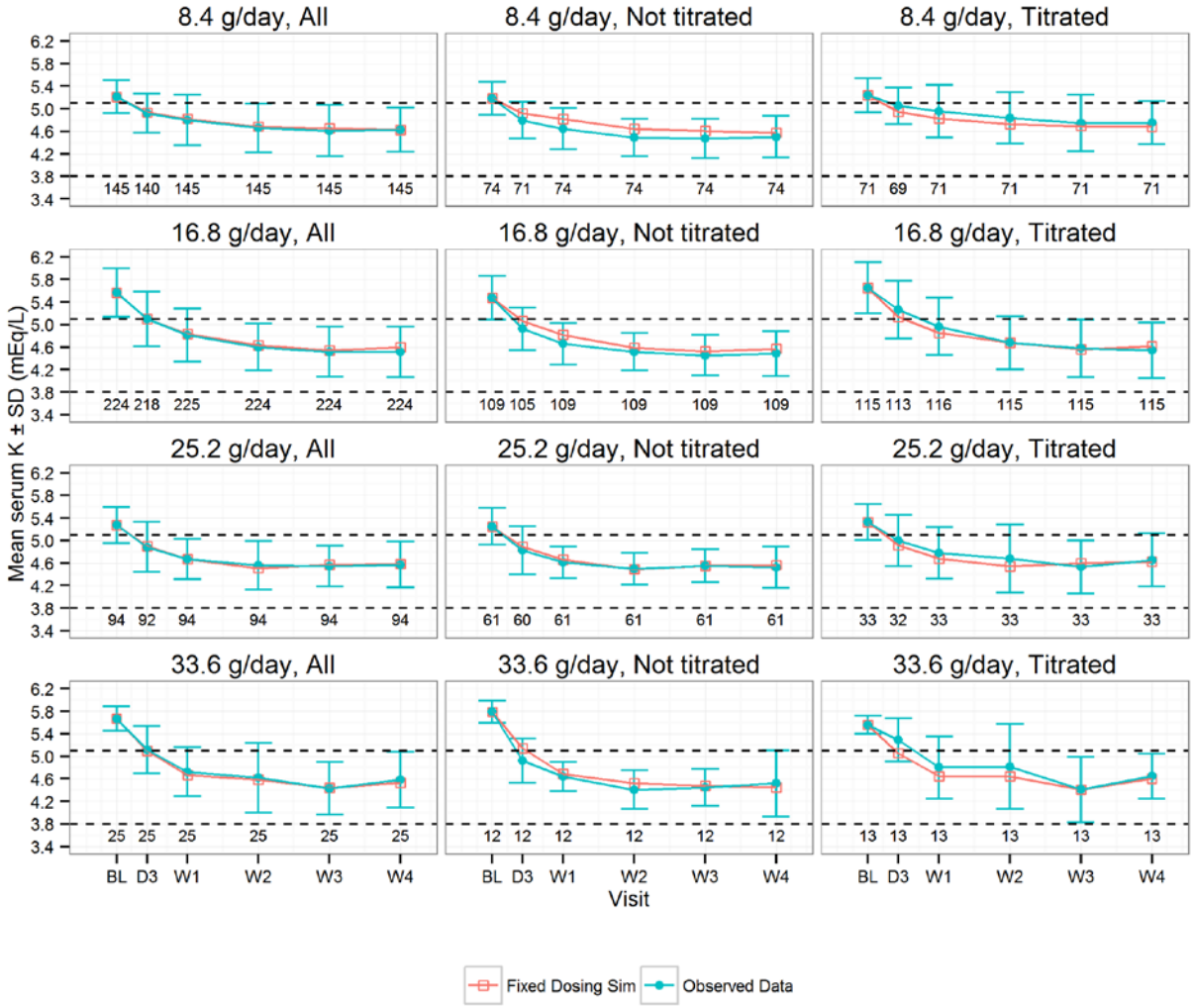
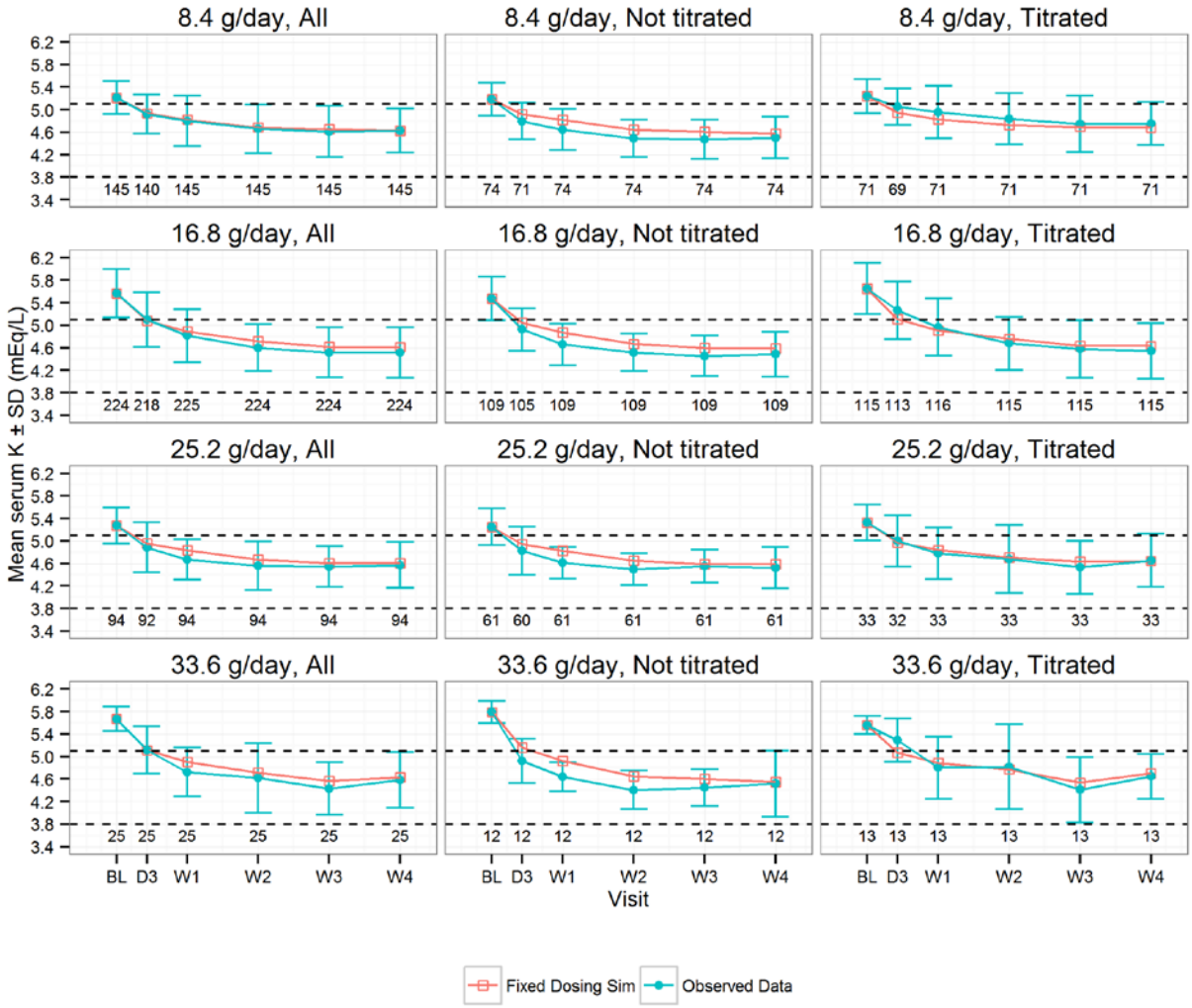


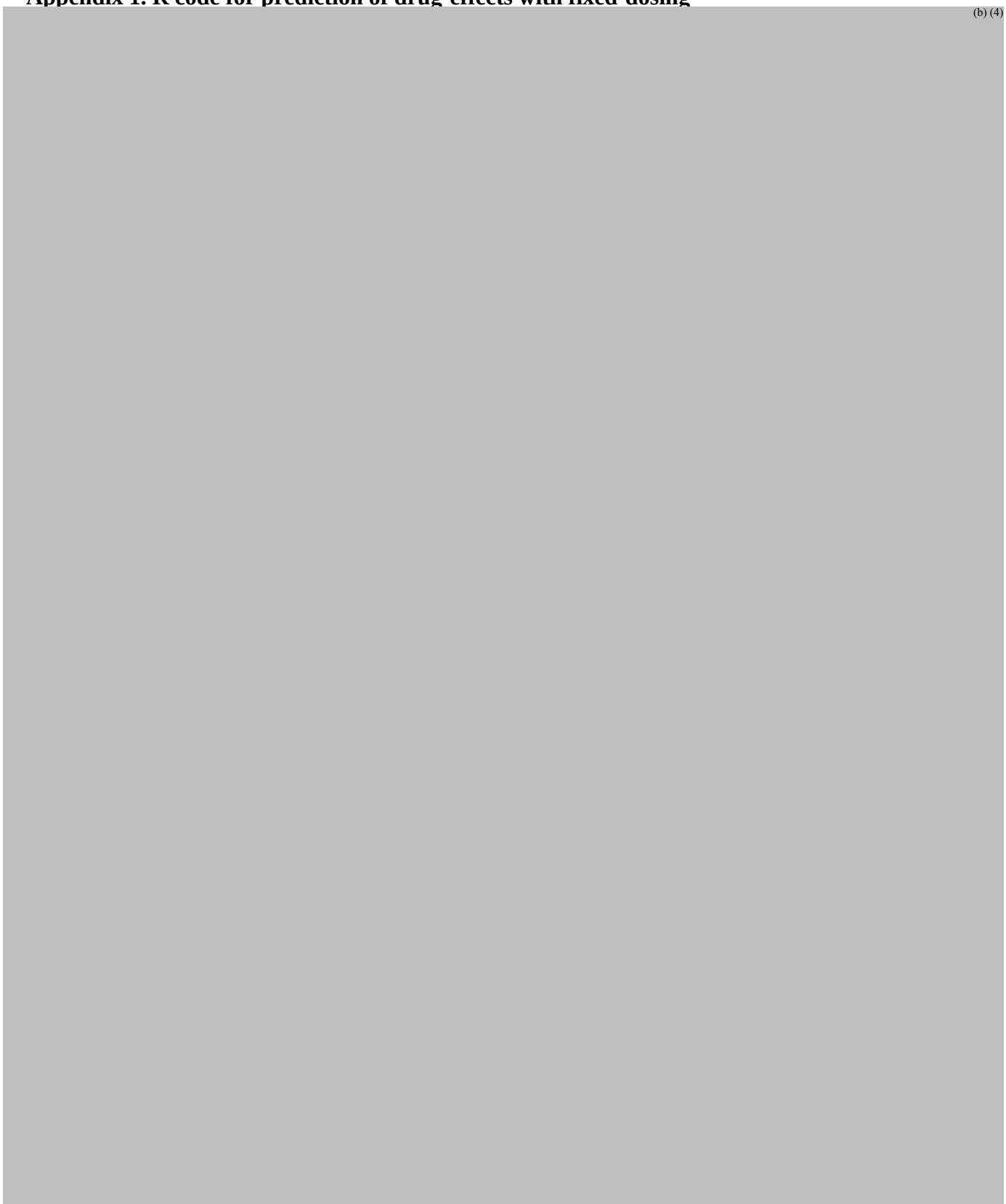
Figure 6 Fixed dosing simulations (dose fixed to 8.4 g/day) based on the prediction methodology described, for either all patients (first column) by starting dose, patients starting and ending on the same dose (not titrated, middle column) by starting dose.



Appendices

Appendix 1. R code for prediction of drug-effects with fixed-dosing

(b) (4)



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10/12/2015

Clinical Pharmacology/Biopharmaceutics Review
Question Based Review (QBR)

PRODUCT (Generic Name):	Patiromer (RLY5016)
NDA:	205-739
PRODUCT (Brand Name):	Veltassa®
DOSAGE FORM:	Powder for Oral Suspension
DOSAGE STRENGTHS:	8.4 g, 16.8 g and 25.2 g patiromer/packet
INDICATION:	Treatment of Hyperkalemia
NDA TYPE:	NME
SUBMISSION DATE:	10/21/2014
SPONSOR:	Relypsa, Inc.
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OCP DIVISION:	DCP 1
OND DIVISION:	DCRP

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1.0 EXECUTIVE SUMMARY

This is an original NDA submitted by Relypsa, Inc., on October 21, 2014 seeking approval of Veltassa® for oral suspension as a potassium binder for the treatment of hyperkalemia. Currently, Kayexalate®, a cation-exchange resin, is the only other potassium binder approved (NDA 011287; approved in 1958) in the US for this indication.

Veltassa® for Oral Suspension contains patiromer sorbitex calcium and xanthan gum. The drug substance, patiromer sorbitex calcium is a new chemical entity where patiromer (active moiety) (b) (4) of the drug substance and is a nonabsorbed, cation-exchange polymer. The proposed product is supplied as a packet containing a powder for oral suspension in water. The packets are available in three strengths that contain 8.4 grams, 16.8 grams, or 25.2 grams patiromer.

The clinical development program in this NDA comprises of eight studies: three Phase 1 studies, four Phase 2 studies and one two-part Phase 3 study (RLY5016-301). A total of 791 subjects participated in these eight clinical studies, including patients with hyperkalemia, chronic kidney disease (CKD), heart failure, diabetes, hypertension and/or patients who were receiving dialysis and healthy volunteer subjects. These studies provide information supporting proof-of-concept (i.e., potassium binding in the gastrointestinal tract), evaluation of dose-response (serum potassium lowering), and support the efficacy and safety of patiromer in the target population for the treatment of hyperkalemia.

The clinical pharmacology program also included evaluation for drug interactions. An *in vitro* test system (spanning the rage of pH in the gastrointestinal tract) was used to evaluate potential interactions between patiromer and 28 orally administered compounds, identified to represent some of the commonly used concomitant medications in the target patient population. This allows for the evaluation of the drug interaction liability of patiromer as a perpetrator, a significant safety concern, and provides information to derive labeling instructions for mitigating the risk.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted in NDA 205-739 and recommends approval of Veltassa® for Oral Suspension for the treatment of hyperkalemia with the following labeling recommendations:

1) Dosing and Administration:
   - A QD regimen is recommended to help mitigate the drug interaction potential with Veltassa®.
   - Treatment should be initiated with a starting dose of 8.4 g/day and should be titrated based on response in increments of 8.4 g/day up to a maximum dose of 25.2 g/day.
   - The titration interval should be at least one week or longer to maximize the effect that can be achieved with the dose. This will also avoid premature uptitrations.

2) Drug Interaction[1]:

- Co-administration of Veltassa® with other drugs should be avoided unless lack of binding to Veltassa® has been demonstrated. When such information is not available maximum separation should be considered given the drug interaction potential.

- If the patient's medications include drugs with a QD dosing regimen, the recommended separation is 12 hours. This recommendation is applicable to situations where the concomitantly administered drugs can be taken together i.e., either in the morning or evening. If the concomitantly administered drugs need to be separated i.e., some taken in the morning and some in the evening, Veltassa® should be administered with lunch i.e., at least 6 hours separation.

- If the patient's medications include drugs with a BID dosing regimen intended for chronic treatment (administered in the morning and evening), Veltassa® should be administered with lunch i.e., at least 6 hours separation.

- If the patient's medications include drugs with a dosing regimen more frequent than BID, a pragmatic separation strategy is not feasible. In such situations, Veltassa® should not be used.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

- Patiromer is a cation-exchange polymer with minimal systemic availability. Hence, conventional absorption, distribution, metabolism and elimination (ADME) aspects do not apply.

- Drug interaction potential of patiromer was evaluated *in vitro*. Twenty eight drugs, identified by the applicant as commonly co-administered medications in the target population were screened for interaction. All interactions below represent the percentage decrease in exposure for the co-administered medication.

    - Greater than 50% interaction was observed in all three media for the following drugs: amlodipine, cinacalcet, ciprofloxacin, levothyroxine, quinidine, trimethoprim.

    - Interaction between 30% and 50% was observed in one media for the following drugs: clopidogrel, lithium, metoprolol, verapamil and warfarin.

    - Less than 30% interaction was observed for the following drugs: allopurinol, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, digoxin, glipizide, lisinopril, phenytoin, rivaroxaban, spironolactone and valsartan.

[1] The specific labeling language is currently being discussed with the review team and discussions are ongoing with the Applicant.

Pharmacodynamics in healthy volunteers

- In a Phase 1 study, patiromer doses administered as thrice daily (TID) over the range of 0 g/day to 50.4 g/day showed dose-dependent increases in mean daily fecal potassium (K) excretion.

- No significant difference in mean daily fecal K was observed following the administration of patiromer at a dose of 25.2 g/day orally as a once daily (QD), or twice daily (BID) or TID regimen. All the treatment regimens showed a significant increase in mean daily fecal K excretion and concomitant decrease in mean daily urinary K excretion. This study provides information supporting QD regimen of patiromer.

Drug effect in patients

- Following a fixed dose of 8.4 g patiromer given BID in CKD patients, statistically significant reductions in serum K were observed as early as 7 hours after the first dose indicating the time to onset of effect.

- Following a BID regimen of patiromer, maximum serum K lowering (steady-state) is attained around 7 – 14 days.

- In a Phase 2 study in CKD patients with hyperkalemia, patiromer doses administered as BID over the range of 8.4 g/day to 33.6 g/day did not demonstrate a clear dose-response relationship for lowering of serum K by Day 3. However, baseline serum K level was identified as the most important predictor of the effect. For the same daily dose, patients with a higher baseline (>5.5 mEq/L) had a greater absolute reduction in serum K compared to those with relatively lower baseline (5.0 mEq/L – 5.5 mEq/L). This information supports initiation of treatment with a dose of 8.4 g/day in all patients regardless of the baseline serum K.

- Based on the integrated efficacy data from Studies RLY5016-301 and RLY5016-205 in patients with a starting dose of 8.4 g/day (N = 145), ~45 % patients achieved the target serum K range of 3.5 mEq/L – 5.0 mEq/L at the starting dose of 8.4 g/day and did not undergo titration, ~30% patients underwent 1 titration step (to a dose of 16.8 g/day) and ~8% patients underwent 2 titration steps (to a dose of 25.2 g/day) to reach the target. None of the patients experienced a serum K lowering of <3.5 mEq/L. So with a starting patiromer dose of 8.4 g/day with titration up to 25.2 g/day, 83% of patients reached the target serum K range.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dosage Form/Strengths: 8.4 g, 16.8 g and 25.2 g patiromer powder/packet

Indication: The proposed indication for Veltassa® (patiromer sorbitex calcium) is for the treatment of hyperkalemia.

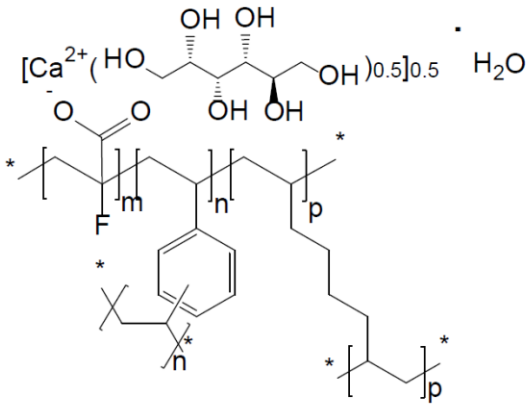
Pharmacologic Class: Potassium binder

Chemical Name: Cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, combination with D-glucitol

Chemical formula: (b) (4)

Molecular Weight ($C_{613}H_{765}F_{114}O_{399}Ca_{57}$): (b) (4)

Chemical structure:



m = number of 2-fluoro-2-propenoate groups m = 0.91

n, p = number of crosslinking groups n + p = 0.09

H_2O = associated water

* = indicates an extended polymeric network

Physico-Chemical Characteristics:

Solubility: Insoluble in water, 0.1 M HCl, methanol and n-heptane

Equilibrium Potassium Binding at pH (b) (4)

[2] No information on the Euilibrium Potassium Binding is available at lower pH.

Formulation: Powder for suspension. The to-be-marketed formulation was used in the pivotal clinical trial.

2.1.2 What is the proposed mechanism of action?

Patiromer sorbitex calcium is a new chemical entity that belongs to the pharmacologic class of potassium binders. Results of the *in vitro* experiments in environments mimicking conditions of the stomach and large intestine provide insights into the mechanism of action. When exposed to an acidic environment, patiromer exchanges the calcium-sorbitex counterion for protons. (b) (4) The lumen of the colon is relatively rich in potassium thus patiromer demonstrates a higher capacity for potassium binding leading to an increase in fecal excretion. This eventually leads to lowering of serum K.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

There are 8 human study reports and an *in vitro* drug interaction screening report (for 28 drugs) submitted to support the dosing and the proposed claim for patiromer (RLY5016).

Four clinical pharmacology study reports were submitted: RLY5016-101, RLY5016-102, RLY5016-103 and RLY5016-201.

Pharmacodynamics in healthy volunteers:

- Study RLY5016-101 evaluated safety, tolerability and dose-response on fecal K excretion following single and multiple doses of patiromer (0 g/day -50.4 g/day administered as TID).
- Study RLY5016-102 compared the K binding effect assessed as fecal K excretion at a patiromer dose of 25.2 g/day administered as TID, BID and QD.

Drug effect in patients:

- Study RLY5016-103 assessed the time to onset of action with four fixed doses of 8.4g administered BID (16.8 g/day).
- Study RLY5016-201 is a phase 2 proof-of concept study in six hyperkalemic hemodialysis subjects.
- Study RLY5016-205 is a Phase 2 dose-ranging study which also contains long term safety information.
- Study RLY5016-301 is the safety and efficacy Phase 3 pivotal study.
- Study RLY5016-202 evaluated the effects of a fixed dose of patiromer (25.2 g/day BID for 28 days) on serum K in normokalemic with heart failure receiving spironolactone treatment.

A brief description of the dose ranging study and the pivotal phase 3 study is presented below:

Dose-Ranging Study (Phase 2)

Study RLY5016-205 (N = 304) is a 1-year, open-label, randomized, Phase 2, dose ranging, efficacy and safety study in which subjects with CKD and hyperkalemia received patiromer. The study had two patiromer treatment periods: a Treatment Initiation Period for 8 weeks, followed by a Long-term Maintenance Period for an additional 44 weeks, allowing treatment with patiromer for up to a total of 1 year. Eligible subjects were assigned to one of two strata according to baseline local laboratory serum K:

- Stratum 1 (serum K values > 5.0 mEq/L to 5.5 mEq/L) subjects were randomized to one of three patiromer starting dose groups: 8.4 g/day, 16.8 g/day, or 25.2 g/day patiromer given as BID
- Stratum 2 (serum K values > 5.5 mEq/L to < 6.0 mEq/L) subjects were randomized to one of three patiromer starting dose groups: 16.8 g/day, 25.2 g/day, or 33.6 g/day patiromer given as BID

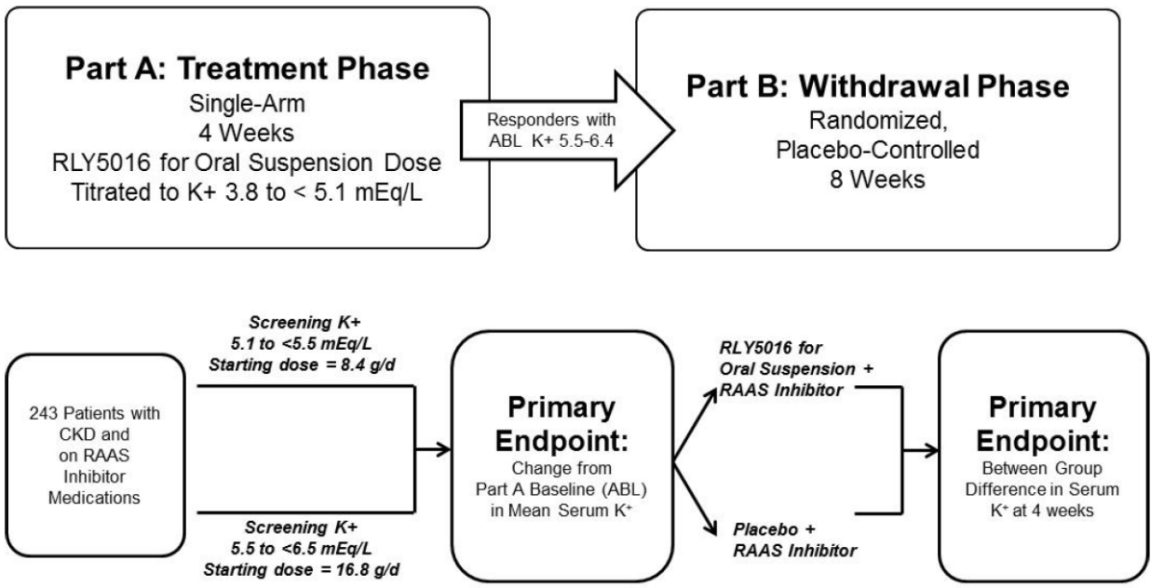
All patiromer doses were administered as equally divided doses twice daily. Doses of patiromer were titrated based on an individual subject's response on day 3 and eventually weekly to achieve and maintain a serum K in the range of 4.0 mEq/L to 5.0 mEq/L during the 8-week Treatment Initiation Period (TIP) and in the range of 3.8 mEq/L to 5.0 mEq/L during the 44-week Long-term Maintenance Period.

The original protocol was designed to enroll non-hyperkalemic subjects who could potentially benefit from initiation or optimization of renin-angiotensin-aldosterone system (RAAS) therapy, and would be eligible for treatment with patiromer if hyperkalemia developed during a run-in period (Cohort 1 and 2). As the study progressed, it became apparent that many subjects who met all other eligibility criteria also already had hyperkalemia, and the protocol was amended to allow these patients to be enrolled directly into the study (Cohort 3). The current review primarily focused on this cohort and conducted additional analyses.

Pivotal Study (Phase 3)

Study RLY5016-301 was a two-part, single-blind, Phase 3 study of patiromer in 243 subjects with hyperkalemia and CKD (Figure 1).

Figure 1: Design of Phase 3 Study RLY5016-301



ABL = Part A Baseline; CKD = chronic kidney disease; K^+= potassium; RAAS = renin angiotensin aldosterone system.
Note: 8.4 g/d = 8.4 g/day patiromer; 16.8 g/d = 16.8 g/day patiromer
Source: *Applicant's Clinical Overview, Figure 6, page 29*

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The Kidney Disease Outcome Quality Initiative (KDOQI) guideline #11[3] states that hyperkalemia due to ACE inhibitors or ARBs is defined as an elevation of serum K concentration to >5.0 mEq/L. The aim of treatment with potassium binders is to achieve control of serum K levels within the normal range of 3.5 mEq/L and 5.0 mEq/L. Consequently, the primary response measure used in the evaluation of effectiveness is the change in serum K. Serum K levels were measured in local as well as a central laboratory by standard validated clinical laboratory methods.

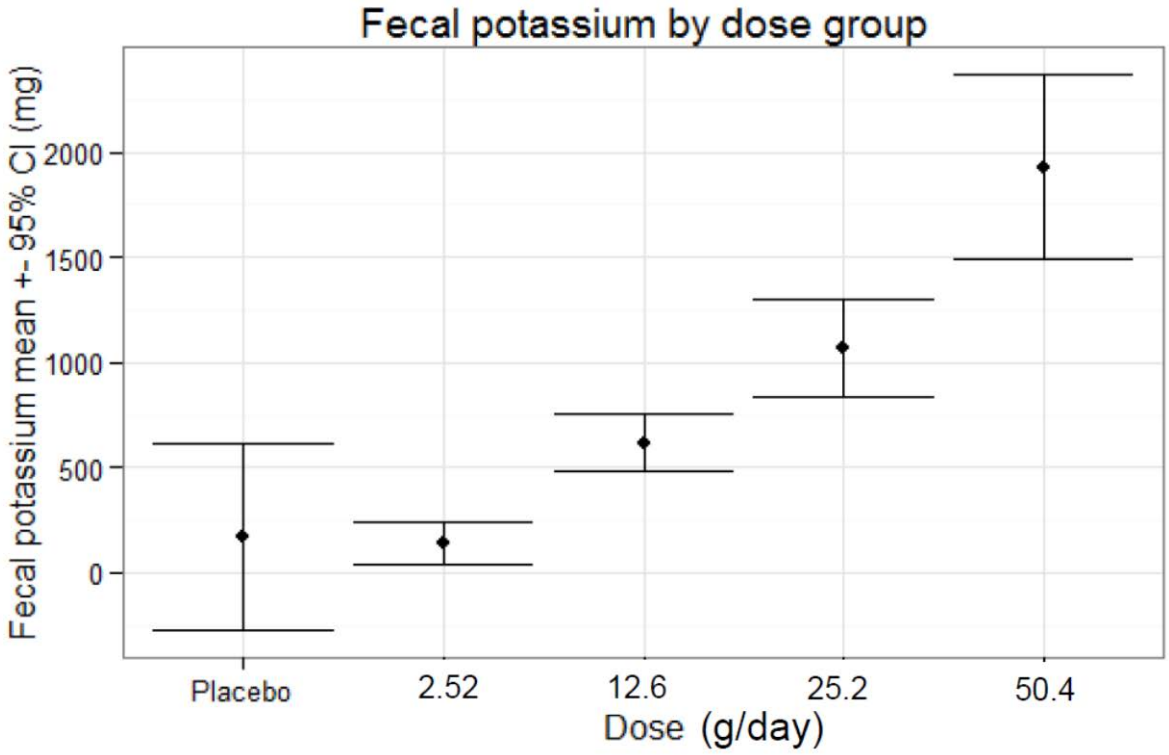
In healthy subjects, serum K levels are not sensitive response measures for evaluating the effect of K binders as the kidney function is intact. However, mean daily fecal K excretion serves as a good measure of drug response in healthy subjects. Daily excretion and mean daily excretion of fecal K were calculated for each healthy subject, separately for the baseline period (4-7 days) and treatment period (4-7 days) collected in 24-hour intervals.

[3] K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. GUIDELINE 11: USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN CKD

2.2.3 What are the characteristics of exposure-response (E-R) or dose-response (D-R) relationships for efficacy and safety?

In healthy subjects, patiromer administered three times a day for 8 days over a dose range of 0 g/day to 50.4 g/day showed a dose-dependent increase in mean daily fecal K excretion (Figure 2). It should be noted that at baseline, there was no statistically significant difference in mean daily fecal K excretion among the treatment groups.

Figure 2: Patiromer (0 g/day - 50.4 g/day administered as TID for 8 days) exhibits a dose dependent increase in mean daily fecal K excretion in healthy subjects



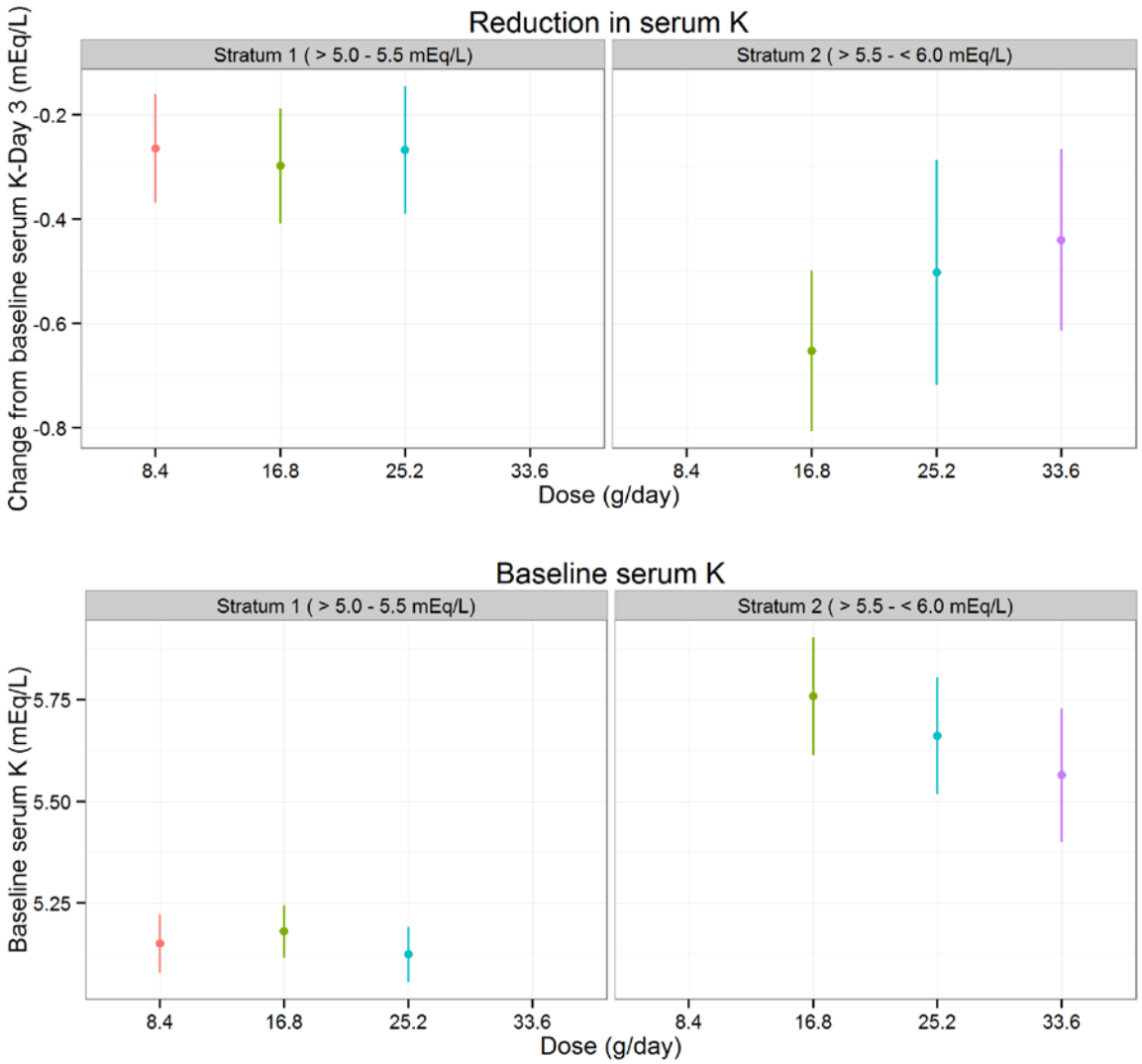
Compared to placebo, patiromer doses of 12.6 g/day to 50.4 g/day showed a nominally significant ($p<0.05$) increase in mean daily fecal K excretion. The lowest patiromer dose of 2.52 g/day was not different from placebo. A corresponding dose-dependent decrease in mean daily urinary K excretion was also observed. Compared to placebo, patiromer doses of 25.2 g/day and 50.4 g/day showed a statistically significant ($p<0.05$) decrease in mean daily urinary K excretion.

In the Phase 2 study, RLY5016-205, CKD patients with hyperkalemia (Cohort 3) were randomized to one of three starting dose levels and stratified by their baseline serum K levels:

- Stratum 1 (serum K values > 5.0 mEq/L to 5.5 mEq/L) patients were randomized to one of three patiromer starting dose groups: 8.4 g/day, 16.8 g/day, or 25.2 g/day patiromer given as BID
- Stratum 2 (serum K values > 5.5 mEq/L to < 6.0 mEq/L) patients were randomized to one of three patiromer starting dose groups: 16.8 g/day, 25.2 g/day, or 33.6 g/day patiromer given as BID

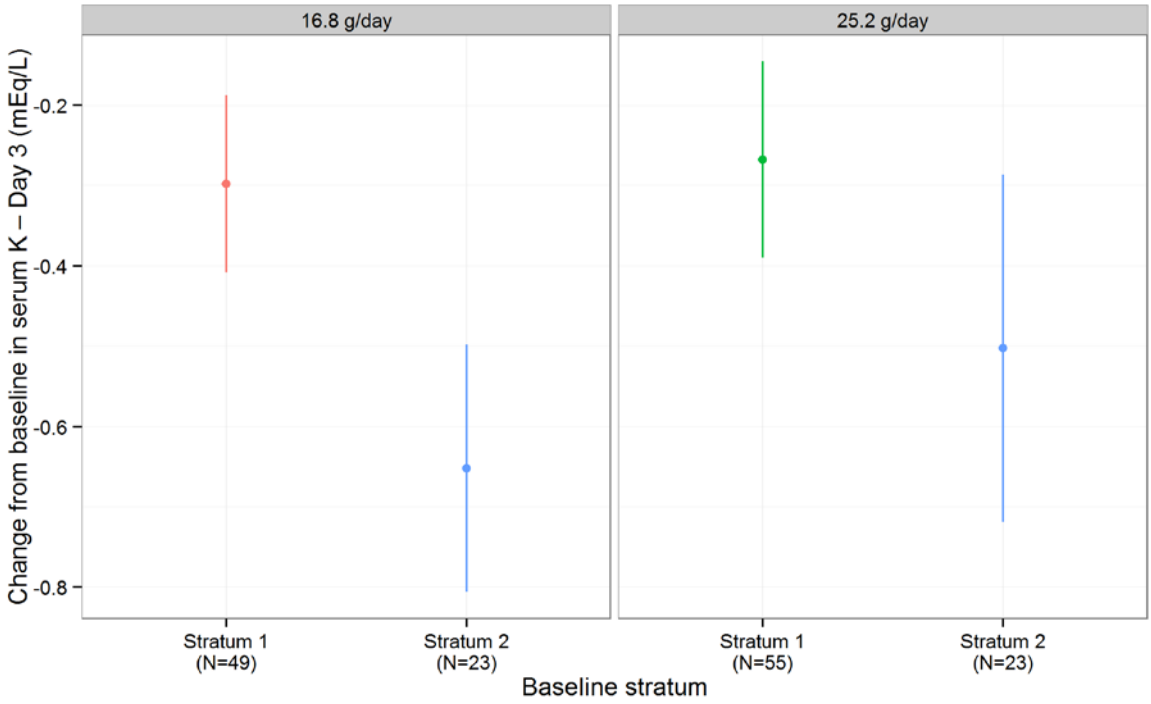
Since dose titration was allowed as soon as day 3, evaluation for dose-response was conducted utilizing day 3 serum K levels as the response measure. As shown in Figure 3 for Stratum 1, there is no apparent dose dependent relationship in lowering of serum K by Day 3. This short duration of treatment may not be sufficient for the manifestation of the full effects associated with each dose level. However, a trend for decrease in effect with increase in dose was observed in Stratum 2. This inverse dose-dependent relationship was primarily driven by differences in the baseline serum K across the different dose groups in Stratum 2 as shown in Figure 3.

Figure 3: No dose dependent lowering of serum K by Day 3. The effect size is dependent on baseline serum K.



For the same daily doses of 16.8 g/day and 25.2 g/day, patients with a higher baseline (Stratum 2) had a greater reduction in serum K compared to those with relatively lower baseline (Stratum 1) (Figure 4).

Figure 4: Baseline Serum K (not the starting patiromer dose) is an important predictor of effect



Taken together, there is no evidence of a dose-response relationship for patiromer to reduce serum K levels by day 3 in hyperkalemia patients. Baseline serum K level (and not the starting dose) is the more important predictor of serum K lowering effect. Similar inference can also be drawn from the over all data (i.e., Cohorts 1 – 3).

In the pivotal phase 3 trial, all patients were started at a dose of 8.4 g/day (Baseline: 5.1 mEq/L to <5.5 mEq/L)) or 16.8 g/day (5.5 mEq/L - <6.5 mEq/L) and titrated based on an individual subject's response on day 3 and eventually weekly to achieve and maintain serum K within a target range of 3.8 mEq/L to < 5.1 mEq/L. The Applicant conducted a mixed model repeated measures (MMRM) analysis of the integrated efficacy data from Studies RLY5016-301 and RLY5016-205 based on the Mid-Cycle Communication on 04/02/2015. This MMRM analysis identified interval baseline, interval dose, interval length, visit, visit by interval baseline interaction and visit by interval dose interaction as the significant predictors of effect. The contribution of baseline serum K to effect was relatively large compared to that of interval dose as shown in Table 1.

Table 1: Model projected mean change in serum K (mEq/L) based on baseline serum K and patiromer dose averaged across visit and interval length effects.

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

For example, based on the model for the same baseline, increase in patiromer dose from 8.4 g/day to 33.6 g/day results in average change from baseline in serum K is ~0.1 mEq/L. However, from the same dose, patients with baseline serum K of 6.0 mEq/L on an average show ~0.6 mEq/L reductions compared to patients with baseline serum K of 5.0 mEq/L.

Dose-Response for Safety / Drop-out

In patients treated with patiromer in the safety and efficacy clinical trials, the most common adverse reactions (>2%) were constipation (7.2%), hypomagnesemia (5.3%), diarrhea (4.8%) and nausea (2.3%). Most of the AEs were characterized as mild or moderate in severity.

In the long term safety study, RLY5016-205, a trend for a dose-dependent increase in hypomagnesemia was observed. While mean reductions in serum magnesium values did not appear to be dependent on the starting dose group, the frequency of hypomagnesemia adverse events was greater in the higher starting dose groups. In the TIP, there appeared to be no dose dependent relationship between the starting dose and the proportion of subjects with hypokalemia (serum K < 3.5 mEq/L).

2.2.4 Is the proposed dosing acceptable?

The applicant's original proposed starting dose was (b) (4) 8.4 grams patiromer (b) (4) with meals, based on serum potassium level (see Table 2 below). Dosage may be adjusted based on the serum potassium level and the desired target range. The dose may be increased or decreased by (b) (4) as necessary, to reach the desired range. If serum potassium is decreasing and approaching (b) (4) dose adjustment may not be necessary.

Table 2: The Applicant's original proposed starting dose for patiromer

Serum Potassium	VELTASSA Dose
(b) (4)	(b) (4)
(b) (4)	8.4 grams (b) (4) a day

* as grams patiromer

The drug interaction profile of patiromer (see Section 2.4.2 for details) is a significant safety concern. (b) (4) The review team considered a QD regimen in an attempt to mitigate a significant part of this liability as this will allow separation by (b) (4) hours of concomitant drug administration where possible (see Section 2.4.2 for details). Based on the review of the information available in the submission, the review team has the following recommendation:

For the treatment of hyperkalemia, the starting dose of patiromer is 8.4 g once daily irrespective of the baseline serum K levels. The dose can be increased or decreased by 8.4 g/day, if necessary, up to a maximum dose of 25.2 g once daily. Dose can be uptitrated in intervals of at least 1-week or longer. The applicant agreed to this recommendation (as indicated in the Late Cycle Meeting Slides submitted on 6/27/2015) and submited an updated labeling reflecting the same (Email communication *via* Project Manager dated 7/17/2015).

The basis for the dosing recommendation is described below:

Dosing Regimen:

Study RLY5016-102 provides an opportunity to evaluate the impact of various dosing regimen on the K binding capacity of the patiromer. This was a Phase 1, open-label, multiple-dose crossover study in healthy subjects (RLY5016-102). A patiromer dose of 25.2 g/day was administered orally as a QD or BID or TID regimen for 6 days in a randomly assigned order.

As shown in Table 3 below, all the dosing regimens demonstrated a significant increase in mean daily fecal K excretion with a corresponding decrease in mean daily urinary K excretion. There was no statistically significant difference among the three dosing regimens with respect to the mean daily fecal or urinary K excretion. This was true for the overall comparison among the 3 dosing regimens, as well as for the pairwise comparisons. Both the sequence and period effects for the analysis of endpoint and change from baseline using the ANOVA model were not significant (at 0.05 level).The mean increase in fecal K excretion ranged from 1283 mg/day to 1550 mg/day, across the three dosing regimens. It should be noted that using a similar study endpoint (fecal K excretion) but different total daily dosing (Question 2.2.3), the endpoint was sensitive enough to differentiate a greater impact on fecal K excretion with increasing total daily dosing. The results from this study demonstrated that the K binding effect of patiromer is similar between BID and QD regimen provided the same total daily dose is administered, thus providing the basis for considering a QD regimen to help mitigate some of the drug interaction liability.

Table 3: Mean (±SD) Daily Fecal and Urinary K Excretion (mg/day) data indicate that the treatment effect is similar among the three dosing regimens. *Samples were collected in 24 hour intervals from Day 3 to Day 6.*

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

Source: *Table recreated from Applicant's Summary-clin-pharm-0002, Table 5, Page 17*

Starting Dose and Maximum Dose:

As discussed in 2.2.3, there is no evidence that higher starting doses are required in patients with a higher baseline serum K. Hence a starting dose of 8.4 g/day should be considered for all patients. A case for a fixed dose without the need for up-titration can be made based on the lack of apparent dose-

response information in hyperkalemia trials. However, given the need to achieve a threshold of 3.8 mEq/L – 5.0 mEq/L, the clinical experience indicates some patients (most likely those with higher baseline serum K) may eventually need higher doses to meet the threshold. Based on the integrated efficacy data from Studies RLY5016-301 and RLY5016-205 in patients with a starting dose of 8.4 g/day, ~45 % patients achieved the target serum K range of 3.8 mEq/L – 5.0 mEq/L at the starting dose of 8.4 g/day, ~30% patients underwent 1 titration step (to a dose of 16.8 g/day) and ~8% patients required 2 titration steps (to a dose of 25.2 g/day) to reach the target. So with a starting patiromer dose of 8.4 g/day with titration up to 25.2 g/day, 83% of patients reached the target serum K range (Table 4). The first up-titration occurred by week 1 in 70% of the patients (40% by Day 3). In approximately 25% of the patients the first up-titration occurred by week 2-3.

Table 4: Most of the patients reach the target serum K with a starting dose of 8.4 g/day and titrated up to a maximum of 25.2 g/day.

Baseline Serum K (mEq/L)	**N**	**Percentage of patients that achieved target serum K (3.8 – 5.0 mEq/L) (%)**			
		8.4 g/day	**16.8 g/day**	**25.2 g/day**	**Total**
5.0-<5.5	117	50	28	9	87
≥5.5	28	29	32	7	68
All	145	46	29	8	83

Despite the limited information in patients with baseline serum K >5.5 mEq/L (N = 28), ~70% of the patients achieved the target starting with a dose of 8.4 g/day with titration up to 25.2 g/day. Further, it can be seen that 30% of the patients with a baseline of serum K >5.5 mEq/L reached the target serum K without the need for up-titration. This is also consistent with the results observed in patients initiated with a starting dose of 16.8 g/day and titrated to 25.2 g/day as shown in table below.

Table 5: In patients with baseline serum potassium >5.5 mEq/L, the proportion of patients reaching target serum K is similar between treatment groups at a starting patiromer dose of 8.4 g/day and 16.8 g/day with titration up to 25.2 g/day.

Starting Dose g/day	**N**	**Percentage of patients that achieved target serum K (3.8 – 5.0 mEq/L) (%)**			
		8.4 g/day	**16.8 g/day**	**25.2 g/day**	**Total**
8.4	28	29	32	7	68
16.8	128	-	40	30	70

Moreover, there is no long-term safety or tolerability experience with unit doses greater than 25.2 g of patiromer. This also limits the maximum dose to 25.2 g administered once daily.

Therefore, a starting dose of 8.4 g/day with the option for dose titration, up to a maximum dose of 25.2 g/day daily should cover the majority of the patients.

Titration Interval:

In the Phase 2 & 3 studies, dose titration was allowed as early as 3 days after the starting of patiromer followed by weekly titration. The adequacy of this titration interval was not justified by the Applicant. Further, no clear instructions are provided in the proposed label on how long patients should wait

following treatment initiation before assessing the need for further dose titration. Hence, additional analysis was performed to evaluate the period of time that should elapse between dose titrations (e.g., titration interval).

To identify the titration interval, the likelihood-based MMRM developed by the Applicant was utilized to characterize the time to steady state effect following fixed dosing. The mean serum K by visit and starting dose are summarized for all subjects completing the 4-week treatment period (N = 488), subjects that underwent titration (N = 232) and subjects that completed the 4 week treatment period at the starting dose i.e., no titration (N = 256).

The simulation of serum K time course following fixed dosing regimen clearly shows that the steady-state effect is generally achieved by 1 – 2 weeks irrespective of the dose. This is also observed in subjects who were not up-titrated (Figure 5) and in subjects who were up-titrated (Figure 6) during the treatment period.

Figure 5: Time course of Mean Serum K (±SD) by starting dose of patiromer for subjects who were not up-titrated during the treatment (N = 256). For simulation, only mean time course following fixed dosing regimen is presented.

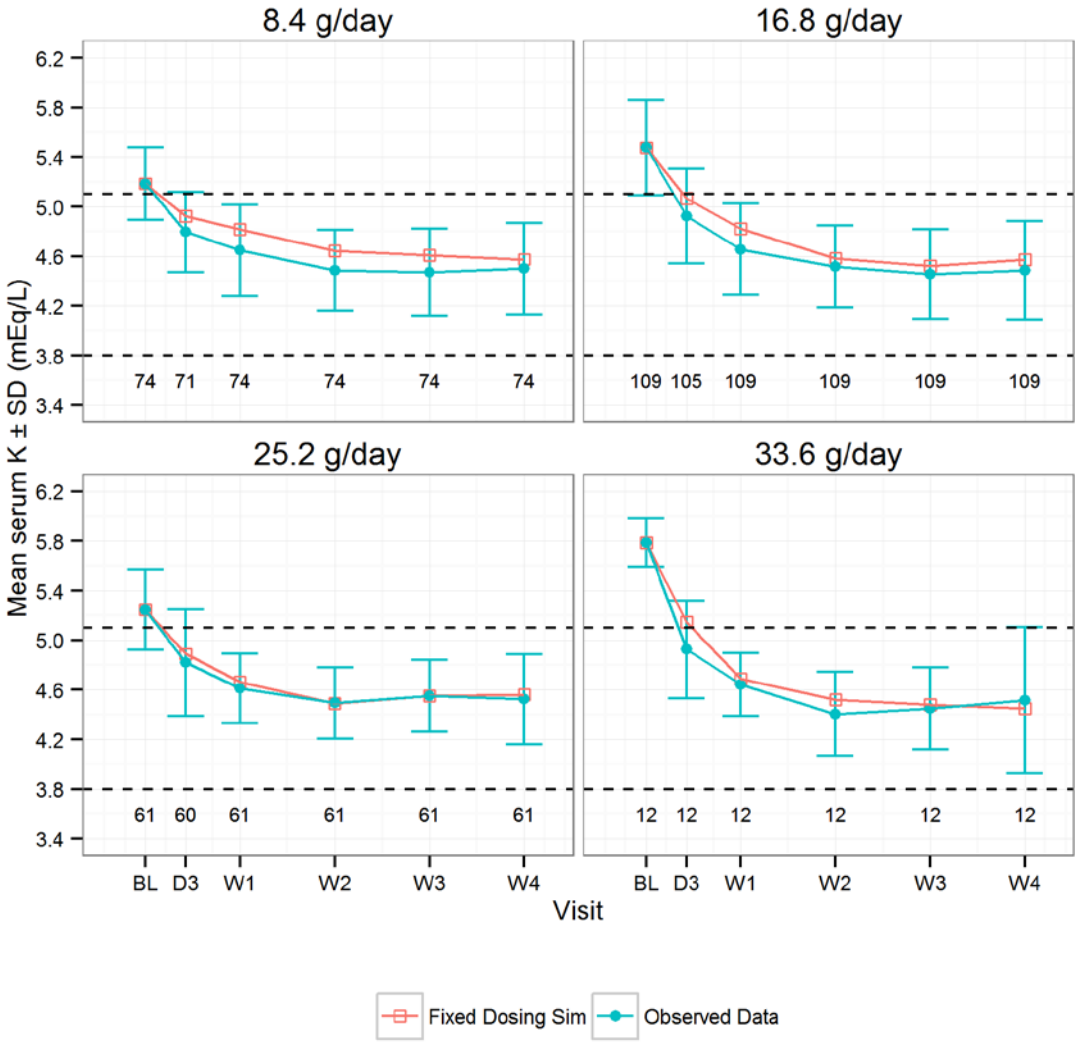
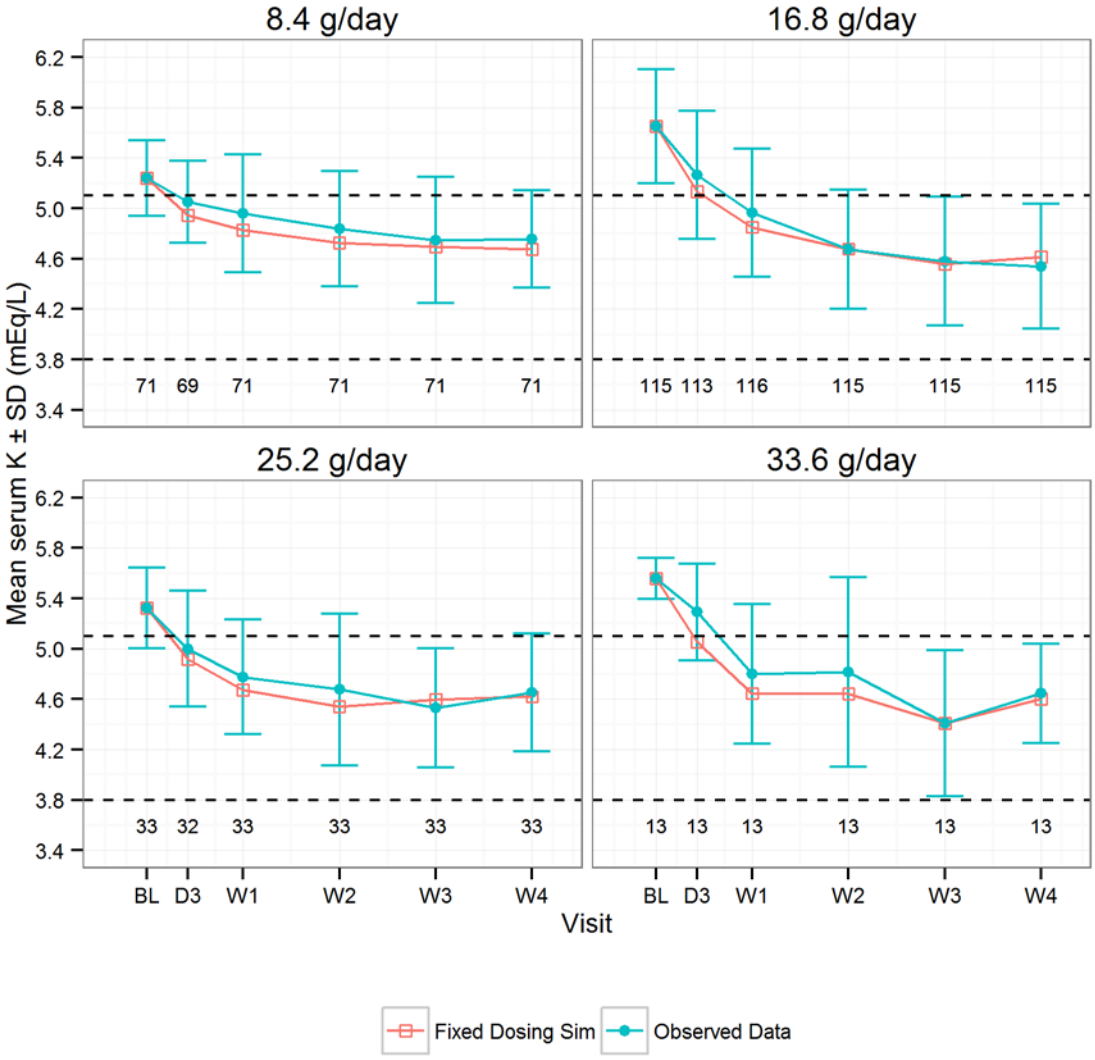


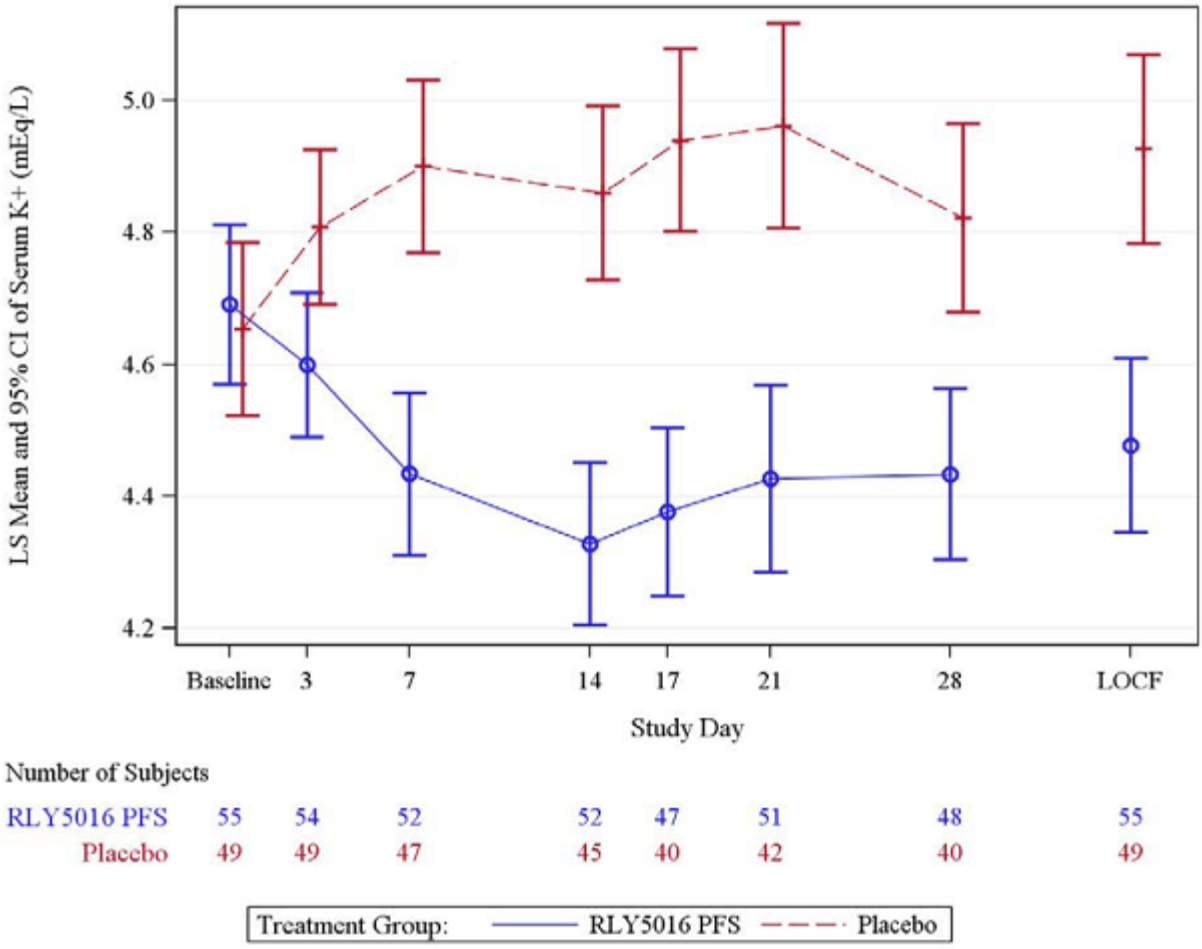
Figure 6: Time course of Mean Serum K (±SD) by starting dose of patiromer for subjects who were up-titrated during the treatment (N = 232). For simulation, only mean time course following fixed dosing regimen is presented.



Further, simulation in the group of subjects who were up-titrated indicates that, titration based on Day 3 serum K levels may be premature. This is evidenced by the similar mean projected serum K for the fixed dosing simulation and that observed following titration (Figure 6).

Lastly, a similar time-course for the evolution of the drug effect is also reported in Study RLY5016 - 202, where patiromer was administered at a fixed dose of 25.2 g/day for 28 days (Figure 7). Consistent with the information generated from the studies in patients with hyperkalemia, the steady-state effects are achieved by Day 14 following the administration of a fixed dosing of patiromer.

Figure 7: Time course of LS Mean and 95% CI of Serum K following fixed dosing with 25.2 g/day of patiromer and placebo in Heart Failure patients.



Source: *Applicant's Study Report - RLY5016-202; Figure 3, page # 83*

Based on the above information and analysis, the review team recommends a titration interval of at least 1 – 2 weeks before considering up-titration. This will avoid premature uptitration as evident in the current development program. Further this titration interval may also aid in mitigating drug interaction liability as it will allow for maximizing the effect on a dose level before up-titration, thus decreasing the potential perpetrator load.

2.2.5 What are the PK characteristics of Patiromer?

No conventional ADME studies were conducted in this submission. This is acceptable as patiromer is a non-absorbed polymer.

2.2.6 What are the PD characteristics of the drug?

The pharmacodynamics characteristics of patiromer except for the onset of effect are described previously (see Questions 2.2.3 and 2.2.4).

The onset of effect was evaluated in a dedicated study in CKD patients receiving 8.4 g BID for two days and the time course of the serum K lowering effects were followed. The serum K decreased following the first dose and a statistically significant difference from baseline were observed as early as 7 hours post dosing. Serum K continues to decrease post dose 2, 3 and 4. The maximum effect in this study was observed at 10 hours following the last dose. After stopping patiromer, serum K levels increased but did not reach the baseline level by day 6. The current study did not evaluate dosing of patiromer to steady-state effects. It should be noted that other studies indicate that it takes at least 1 – 2 weeks of treatment at a given dose level of patiromer to achieve maximum effects.

2.3 INTRINSIC FACTORS

Intrinsic factors are not expected to impact the availability of patiromer at the site of action and hence not evaluated.

2.4 EXTRINSIC FACTORS

Patiromer is not expected to have systemic absorption. No conventional clinical pharmacology studies were conducted in this submission to evaluate the impact of other drugs on patiromer. The focus in this NDA was on the potential for patiromer to bind concomitantly administered drugs in the GI tract thereby resulting in reduced bioavailability of the concomitantly administered drugs and consequently loss of efficacy. The underlying conditions that are common causes of hyperkalemia in the clinical setting are primarily CKD and heart failure with concomitant use of Renin-Angiotensin-Aldosterone System inhibitors (RAASi) medication. As such the patient population is prescribed multiple medications. This is also a large population and as such the potential for drug interaction with a drug that is proposed to be administered (b) (4) represents a significant safety issue.

2.4.1 Is patiromer a substrate, inhibitor or inducer of CYP enzymes and/or transporters?

The potential of patiromer to be a substrate, inhibitor or inducer of CYP enzymes and/or transporters is expected to be minimal and was not evaluated in this NDA.

2.4.2 Is there an in vitro basis to suspect drug-drug interaction?

Yes. *In vitro* studies were conducted under conditions which mimic pH and cation conditions in different regions of the gastrointestinal tract. Testing was conducted in aqueous solutions of pH 1.2, 4.5 and 6.8 with incubation at 37°C for 3 hours. Each test drug was evaluated in 12 replicates in the presence or absence of patiromer. The amount of the concomitant drug remaining at the end of the incubation was measured to evaluate the extent of binding to patiromer. The results of the *in vitro* screening are categorized into 3 classes based on the extent of interaction.

As shown in Table 6 below extensive binding (at least 50%) was observed for 7 drugs in all three media.

Table 6: Test Drugs that demonstrate at least 50% interaction with patiromer in all matrices. *Note: The table shows % amount of the test drug remaining after incubation with patiromer.*

Test Drug	Predicted Charge at pH 3.0 – 5.9[a]	In Vitro Binding (90% CI)[b]		
		SGF + 0.05% Tween-20	Acetate Buffer + 0.05% Tween-20	SIF + 0.05% Tween-20
Amlodipine	Positive	10.3, 11.4	35.3, 38.0	12.5, 13.6
Cinacalcet	Positive	13.0, 13.8	19.0, 19.7	17.7, 19.0
Ciprofloxacin	Positive	17.4, 18.6	23.8, 25.8	6.3, 7.5
Levothyroxine	Zwitterionic	ND[c]	ND[c]	ND[c]
Quinidine	Positive	11.9, 13.3	42.2, 44.0	22.9, 25.7
Thiamin	Positive	28.6, 28.9	50.0, 51.3	42.2, 43.5
Trimethoprim	Positive	35.4, 37.1	54.8, 55.8	27.9, 28.9

Source: *Applicant's Study report RLY-tr-0130, Table 10, Page 26*

As shown in Table 7, another 7 drugs showed 30% - 50% binding in at least one of the testing media.

Table 7: Test Drugs that demonstrate 30% - 50% interaction with patiromer in one of the matrices. *Note: The table shows % amount of the test drug remaining after incubation with patiromer.*

Test Drug	Predicted Charge at pH 3.0 – 5.9[a]	In Vitro Binding (90% CI)[b]		
		SGF + 0.05% Tween-20	Acetate Buffer + 0.05% Tween-20	SIF + 0.05% Tween-20
Clopidogrel	Positive at pH 3.0 – 4.5; Neutral at pH 5.9 and above	***65.5, 66.5***	ND[c]	ND[c]
Furosemide	Neutral at pH 3.0; Negative at pH 4.5 and above	***66.7, 67.8***	94.0, 95.1	74.5, 84.1
Lithium	Positive	92.9, 93.7	88.4, 89.1	***56.8, 57.1***
Metformin	Positive	***47.9, 49.9***	80.1, 83.5	78.4, 82.0
Metoprolol	Positive	71.3, 72.2	84.4, 87.5	***67.7, 69.6***
Verapamil	Positive	***50.7, 52.7***	88.1, 89.1	77.0, 78.8
Warfarin	Neutral at pH 3.0 – 4.5; Negative at pH 5.9 and above	***65.5, 67.2***	91.7, 93.3	95.8, 98.8

Source: *Applicant's Study report RLY-tr-0130, Table 11, Page 27*

Lastly of the 28 drug screened for interaction, 14 showed < 30% interaction as shown in Table 8 below. The threshold of no clinical concern at 30% is generally applicable for drugs with a broad therapeutic index. However, this will not be applicable for drugs with a narrow therapeutic index or if a significant loss in efficacy is expected from small decrements in exposure. From this perspective, the 28.5% binding observed between rivaroxaban and patiromer could be considered a clinically relevant interaction. An interaction resulting in decreased systemic exposure will increase the risk for ischemic stroke, an unacceptable liability. Instructions/approaches to mitigate the interaction potential should also be provided for rivaroxaban. Other than rivaroxaban, drugs that showed < 30% interaction can be used with patiromer and no dose adjustment is warranted.

Table 8: Test Drugs with < 30% Interaction with Patiromer in All Matrices. *Note: The table shows % amount of the test drug remaining after incubation with patiromer.*

Test Drug	Predicted Charge at pH 3.0 – 5.9[a]	In Vitro Binding (90% CI)[b]		
		SGF + 0.05% Tween-20	Acetate Buffer + 0.05% Tween-20	SIF + 0.05% Tween-20
Allopurinol	Neutral	85.2, 86.2	86.2, 94.3	90.0, 98.6
Amoxicillin[c]	Zwitterionic	ND	97.3, 101.2	94.9, 104.2
Apixaban	Neutral	75.3, 76.0	97.0, 97.5	97.6, 98.0
Aspirin	Neutral at pH 3.0; Negative at pH 4.5 and above	100.5, 100.8	98.9, 100.7	99.5, 100.4
Atorvastatin	Neutral at pH 3.0; Negative at pH 4.5 and above	89.0, 93.4	92.2, 94.4	96.4, 106.0
Cephalexin	Zwitterionic	88.3, 89.1	92.5, 97.4	102.5, 106.3
Digoxin[c]	Neutral	ND	107.5, 111.1	100.7, 106.3
Glipizide	Neutral at pH 3.0 – 4.5; Negative at pH 5.9 and above	72.2, 73.6	96.2, 96.9	97.0, 100.0
Lisinopril	Zwitterionic	77.5, 78.3	98.3, 103.1	97.0, 100.0
Phenytoin	Neutral	81.7, 85.2	89.6, 90.7	84.6, 101.7
Riboflavin[d]	Neutral	93.5, 97.8	ND	94.6, 98.4
Rivaroxaban	Neutral	71.5, 72.3	92.7, 93.1	94.9, 95.4
Spironolactone	Neutral	78.0, 79.4	97.2, 99.9	95.2, 98.5
Valsartan	Neutral at pH 3.0; Negative at pH 4.5 and above	85.5, 87.3	100.9, 101.9	97.1, 98.9

Source: *Applicant's Study report RLY-tr-0130, Table 12, Page 29*

Labeling Strategy:

Instructions for co-administration with these drugs where a clinically relevant interaction (Table 6, Table 7 and rivaroxaban) is identified needs to be provided in the label. The general strategy for mitigating an interaction would be to separate the timing of administration of concomitantly administered drugs with patiromer. The duration of the separation will depend on the absorption kinetics of the concomitantly administered drug. Such an approach has previously been used to address the interaction potential for some of the recently approved phosphate binders. This was feasible as the number of interactions were few, unlike the current situation where at least 50% of the tested drugs have demonstrated the potential for a clinically significant interaction. Further, managing the interaction liability on a drug to drug basis results in a wide range of labeling instructions (separation ranging from 2 hrs to 8 hrs). This approach is not pragmatic for the current situation and will likely lead to medication errors. Moreover, this approach will not address the interaction potential with drugs that were not evaluated.

The review team believes a QD dosing regimen (agreed to by the applicant) of patiromer should provide a general mitigation pathway for most of the drugs. This approach is generally applicable to most concomitantly administered drugs with a QD regimen and will ensure at least 12 hour separation. The recommendations proposed by the review team are listed below:

- Co-administration of Veltassa® with other drugs should be avoided unless lack of binding to Veltassa® has been demonstrated. When such information is not available maximum separation should be considered given the drug interaction potential.
- If the patient's medications include drugs with a QD dosing regimen, the recommended separation is 12 hours. This recommendation is applicable to situations where the concomitantly administered drugs can be taken together i.e., either in the morning or evening. If the concomitantly administered drugs need to be separated i.e., some taken in the morning and some in the evening, Veltassa® should be administered with lunch i.e., at least 6 hours separation.
- If the patient's medications include drugs with a BID dosing regimen intended for chronic treatment (administered in the morning and evening), Veltassa® should be administered with lunch i.e., at least 6 hours separation.
- If the patient's medications include drugs with a dosing regimen more frequent than BID, a pragmatic separation strategy is not feasible. In such situations, Veltassa® should not be used.

The review team believes that communication of the risk can alleviate some of this safety concern. In addition to highlighting this risk in the Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology sections, the Division is considering a Boxed Warning and Medication Guide (outside of a Risk Evaluation and Mitigation Strategy). A request was sent to the applicant to propose a pragmatic strategy to mitigate the potential risk of drug-drug interactions. The updated proposal is not yet available at the time of this review.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The final to-be-marketed formulation was used in the pivotal clinical trial. In addition, the product is not expected to be absorbed. Hence, bioequivalence studies were not conducted.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay methods for drugs tested in the *in vitro* DDI studies are acceptable. Concentrations of drugs in *in vitro* testing media were determined using reversed phase high performance liquid chromatography (HPLC) for 24 tested drugs, liquid chromatography-mass spectrometry (LC/MS-MS) methods for atorvastatin and digoxin and ion chromatography for lithium. All analytical methods were qualified to demonstrate specificity, linearity, accuracy and precision, and stability.

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/s/

JU PING LAI
07/22/2015

JEFFRY FLORIAN
07/22/2015

RAJANIKANTH MADABUSHI
07/23/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205739	**NDA Submission Type**	NME
OCP Division	I	**Brand Name**	Veltassa
Medical Division	DCRP	**Generic Name**	Patiromer sorbitex calcium
OCP Reviewer	Ju-Ping Lai	**Drug Class**	Potassium binder
OCP Team Leader	Rajanikanth Madabushi	**Indication(s)**	Treatment of hyperkalemia
Pharmacometrics Reviewer	--	**Dosage Form/Strength**	Powder for suspension/ (b) (4) 8.4, (b) (4) 16.8, (b) (4) or 25.3 gram
Date of Submission	10/21/2014	**Dosing Regimen**	**Starting:** The proposed starting dose is (b) (4) 8.4 grams patiromer (b) (4) with meals, based on serum potassium level. **Titration:** Doses may be increased or decreased by (b) (4), as necessary, to reach the desired serum potassium range.
OCP Review Due	06/21/2015	**Route of Administration**	Oral
AC Meeting	--	**Sponsor**	Relypsa, Inc.
PDUFA Due Date	10/21/2015	**Priority Classification**	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

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In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	**X**	**2 (28 drugs)**		Screening for potential DDIs
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Healthy Volunteers - Phase 1:	**X**	**2**		101(SAD, MAD); 102(TID,BID,QD)
Hyperkalemia and CKD - Phase 1:	**X**	**1**		103 (time to onset of action)
Phase 2:	**X**	**2**		201 (Hemodialysis patients); 205 (Dose-ranging)
Phase 3:	**X**	**1**		301 (4 weeks efficacy+ 8 weeks withdraw)
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Pop PK				
Pop PK/PD				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	TBM product used for Phase III pivotal trial
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize			X	No human PK;

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	the drug product, or submit a waiver request?				No absorption based on radiolabeled ADME studies in animals.
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			Datasets are available in .xpt format for pivotal studies
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			
	Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
	Data				
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
13	Is the appropriate pharmacokinetic information submitted?			X	No human PK; No absorption based on radiolabeled ADME studies in animals.
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal	X			

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	studies)?				
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
17	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	No absorption based on radiolabeled ADME studies in animals.
	General				
20	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

Ju-Ping Lai 12/04/2014
Reviewing Clinical Pharmacologist Date

Rajanikanth Madabushi 12/04/2014
Team Leader/Supervisor Date

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

/s/

JU PING LAI
12/18/2014

RAJANIKANTH MADABUSHI
12/18/2014