CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205739Orig1s000

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 205739 (patiromer; Veltassa)

Sponsor: Relypsa

Review date: 17 October 2015

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Patiromer is a (b) (4) polymer (b) (4) intended as a non-absorbable potassium binder.

The application has been the subject of reviews of CMC/Biopharmaceutics by Drs. Frankewich, Sapru, Chikhale, Srinivasachar and others (28 July 2015; 15 October 2015), a pharmacology/toxicology review by Dr. Link (19 June 2015), clinical pharmacology reviews by Drs. Lai, Florian, and Madabushi (23 July 2015; 16 October 2015), clinical review by Dr. Xiao (19 June 2015), and statistical review by Dr. Kong (11 June 2015). There is a CDTL memo by Dr. Thompson (9 October 2015) with which I am in substantial agreement. I note a few selected issues here.

At this writing, there are no open CMC issues. The drug product must be refrigerated to retard fluoride release, and then used within 3 months of being stored outside a refrigerator at room temperature (25°C ± 2°C [77°F ± 4°F]). However, the sponsor printed carton and container labels with instructions (b) (4). CMC's position (email of 15 October) is that the carton and container labels need to be consistent with the PI. I agree that the carton and container labels need to be made consistent, but I believe that this can reasonably be deferred until the next printing. I do not believe that storage under the conditions on the carton and container label is less safe (b) (4)

Manufacturing inspections were satisfactory.

Radiolabel studies in animals confirm lack of absorption of patiromer; for this reason carcinogenicity (and QT) studies were waived, but long-term studies reveal no concern about GI irritation that might lead to local, GI cancer.

The binding capacity of patiromer is said to be (b) (4), but in a phase I study[2], normal subjects who were presumably at steady-state were excreting about 120 mEq per day, 90% in urine and 10% in feces, and patiromer 25 g shifted only about 1/3 of this from urinary to fecal excretion, i.e., corresponding to only about 1.5 mEq/g.

Potassium excreted by the kidney is derived from the intravascular compartment. The amount of potassium in this compartment is on the order of 4-5 mEq/L x 5 L or 20-25 mEq; thus, even with an effective binding capacity of 1.5 mEq/g, patiromer displaces more potassium in a day than is contained in the entire intravascular compartment.

Giving the same dose once, twice, or three times a day gave similar binding, which is consistent with potassium uptake and the binding to patiromer taking place in the colon. On fixed doses of 8 to 33 g/day, subjects with serum potassium in the range of 5 mEq/L had declines in serum potassium to new steady-state levels with a half-life of 3-

(b) (4)

[2] *Table 3, page 13 of the clinical pharmacology review and Table 1, page 6 of the CDTL review.*

4 days[3]. Following withdrawal after treatment for a year, plasma potassium levels recover with about the same time constant[4]. Unlike a person with normal renal function, someone with significant renal impairment cannot keep up with high potassium load, so a binder at least temporarily puts him into net negative potassium balance, but the amount removed is so small—in comparison to the 2500 or so mEq in the intracellular space—that the reduction in serum potassium appears to be a linear but shallow function of exposure, only about 0.1-0.2 mEq/L/day.

Patiromer doses up to 50 g/day result in approximately linear increases in fecal excretion of potassium[5]. Projected changes in serum potassium[6] are not only quite shallow, but they are also much less than linear. You do, however, get larger effects the more hyperkalemic one is, which seems like a useful attribute. Hypokalemia was uncommon in clinical studies.

Aside from equilibration time, the nature of the flux between the intravascular and intracellular compartments is not well characterized in these studies. With renal clearance capacity to spare, one clearly can accommodate considerable latitude in potassium intake (go days without intake) or absorption (diarrhea or binder) with little change in serum potassium. How the set-point for serum potassium is impacted by GFR and net potassium load is not so clear, but the approach to dose titration every week or two seems pragmatic.

The most commonly reported adverse effects (<10%) were GI symptoms that often resolved with continued treatment. The main safety issue is the potential for drug interactions through non-specific binding. Neither clinical study data nor post-marketing data are going to be good for detecting such problems, because many drugs do not have large enough treatment effects to be observable by an individual. This issue is well analyzed in Dr. Thompson's CDTL memo. I believe that the best chance for managing this risk is to avoid taking patiromer within 6 hours of *any* other drugs. This strategy, if followed, would adequately protect against interactions involved drugs that are absorbed in the *anterior* GI tract. It clearly would not work if there were a drug that was mainly absorbed from the posterior GI tract.

Getting other drugs separated in time of administration from patiromer will be less reliable as new drugs are added to a patient's regimen, and more prescribers are involved. I had advocated for short-term, episodic use, to limit the chances for new drugs to be introduced without proper timing relative to patiromer. I no longer think that is viable, considering how the drug will likely be used—in a setting with chronic hyperkalemia. The team is exploring whether pharmacy dispensing systems can be programmed for a general alert of this nature.

Hyperkalemia is a self-evident surrogate end point. Neither the review team nor I question the importance of its treatment to reduce the risk of cardiac arrhythmia.

Labeling that I am forwarding generalizes the warning about taking patiromer closer than 6 hours to other drugs. In fact, it discourages other behavior by failing to disclose which drugs appear not to bind patiromer, although, of course, such information is available in reviews.

At this writing, the sponsor has agreed neither to the 6-hour separation (the rationale for which is documented in the final clinical pharmacology memo) nor to such

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[3] *Figure 5, page 15 of the clinical pharmacology review. A similar time course is shown with 25 g/day in the study shown in Figure 7, page 17.*

[4] *Study illustrated in Fig 5, page 15 of the CDTL memo.*

[5] *Figure 2, page 9 of the clinical pharmacology review.*

[6] *Table 1, page 11 of the clinical pharmacology review.*

generalization for all orally administered drugs. I expect agreement will be forthcoming, but I would issue a complete response without both elements in labeling.

We have also somewhat simplified instructions for creating and administering a slurry of patiromer in water. This could be further simplified. The basic idea is to get the powder ingested without a lot of water. Labeling could just say that and let patients/caregivers figure it out.

SPS, the only other approved potassium binder, could well have similar drug interaction issues, but it has not been adequately studied. (b) (4)

Kellie Taylor has explored how drug interaction data are made available to retail pharmacists. We probably need to follow-up a few months after approval to see what the pharmacy information systems did with patiromer.

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

/s/

NORMAN L STOCKBRIDGE
10/17/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-739
Priority or Standard	Standard
Submit Date(s)	October 21, 2014
Received Date(s)	October 21, 2014
PDUFA Goal Date	October 21, 2015
Division / Office	DCRP/ODEI/OND
Reviewer Name(s)	Shen Xiao M.D, PhD
Review Completion Date	June 19, 2015
Established Name	Patiromer sorbitex calcium (RLY5016)
(Proposed) Trade Name	Veltassa™
Therapeutic Class	Potassium binder
Applicant	Relypsa, Inc
Formulation(s)	Suspension solution
Dosing Regimen	Powder: (b) (4) 8.4, (b) (4) 16.8, (b) (4) and 25.2 grams patiromer packets.
Indication(s)	Treatment of Hyperkalemia
Intended Population(s)	Adult patients with hyperkalemia

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Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CK	creatine kinase
CKD	chronic kidney disease
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
DDI	drug-drug interaction
DS	drug substance
DBP	diastolic blood pressure
ECG	electrocardiogram
ESRD	end stage renal disease
EU	European countries
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HD	hemodialysis
HF	heart failure
ICH	International Conference on Harmonization
iPTH	intact parathyroid hormone
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
KDOQI	Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney Disease Improving Global Outcomes
LD	low dose

LOCF	last observation carried forward
LSM	least squares mean
MCHC	mean corpuscular hemoglobin concentration
MD	maintenance dose
MI	myocardial infarction
MRI	magnetic resonance imaging
NDA	New Drug Application
NS	not significant
OSI	Office of Science Investigation
PD	Peritoneal dialysis
PK	pharmacokinetic
PTCA	percutaneous coronary angioplasty
QD	once a day
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SPA	special protocol assessment
TEAE	treatment-emergent adverse events
TSAT	transferrin saturation
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend that Veltassa™ (RLY5016, patiromer sorbitex calcium) be approved for the treatment of hyperkalemia in adults if the potential risk of drug-drug interactions can be adequately addressed.

1.2 Risk Benefit Assessments

Veltassa demonstrated clinically and statistically significant reductions in serum potassium levels and enabled the majority of subjects to reach and/or remain in the target range of potassium in the pivotal efficacy trial and other efficacy studies. The potassium lowering effect of RLY5016 is maintained over time (for at least 12 months). The ability to titrate RLY5016 also provides the prescribing clinician flexibility to individualize dosing to achieve larger or smaller potassium reductions in response to changes in the patient's serum potassium levels and underlying clinical state. The time of onset of action (~ 7 hours) limits the utility of this therapy in settings where potassium must be acutely lowered.

The major safety concern with Veltassa is the potential for clinically important drug-drug interactions. Of the 28 compounds that underwent in vitro screening, seven (Amlodipine, Cinacalcet, Ciprofloxacin, Levothyroxine, Quinidine, Thiamine and Trimethoprim) showed > 50% binding to RLY5016 and another seven (Clopidogrel, Furosemide, Lithium, Metformin, Metoprolol, Verapamil and Warfarin) showed 30% to 50% binding. The Agency has asked the applicant to propose a pragmatic strategy to mitigate the potential risk of drug-drug interactions. The proposed strategy should be reasonably easy to implement and should be applicable to a wide variety of medications that are commonly used in the target population.

Interpretation of the safety database is limited by the lack of a control arm in many of the studies; however, the drug is not significantly absorbed and so a controlled safety database is perhaps less critical in this setting. In the clinical trials, drug-related adverse events (AEs) were primarily limited to GI effects and hypomagnesaemia. Constipation, hypomagnesaemia and diarrhea were the most common RLY5016-related AEs and were reported in 7.2%, 5.3%, and 4.8% of subjects respectively. Other common drug-related GI AEs included nausea (2.3%), flatulence (2.0%) and vomiting (1.8%). The majority of the GI AEs occurred early after starting treatment (within four weeks), were mild in severity, and resolved with continued treatment. While AEs of hypomagnesaemia were reported in approximately 5% of subjects, no subject developed a serum magnesium level less than 1.0 mEq/L and no subject discontinued treatment due to hypomagnesaemia. Of note, hypokalemia, a potential risk, was uncommon with the dosing regimen used in the phase 3 trial, which included titration based on response. The overall incidence of hypokalemia in the studies was 1.5%.

Fluoride is a degradation product of RLY5016 and so fluoride absorption resulting in accumulation of fluoride was a potential safety concern. Serum fluoride levels were evaluated at baseline and periodically in the clinically trials. In the pooled studies, mean increases in serum fluoride ranging from (b) (4) were observed at Weeks 1, 4, 8, 12 and the last measurement. There was no clear dose-response relationship. According to the published literature, serum fluoride levels (b) (4) may lead to adverse effects if such exposure is maintained over the long-term (i.e., months to years). In this context, the reported changes in fluoride levels seen in subjects on RLY5016 do not appear to be clinically meaningful. No fluoride accumulation related AEs were observed in a study of up to one year duration, however the size and the duration of the trial (as well as the lack of a control arm), limit interpretation of these data.

Overall, the potential for drug-drug interactions remains a significant safety concern. Beyond this issue, RLY 5016 has a favorable benefit/risk profile as a treatment for hyperkalemia

1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Post market Requirements and Commitments

Pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) should be deferred until after approval. There are ongoing discussions with the applicant about the design of their pediatric development program.

2 Introduction and Regulatory Background

2.1 Product Information

Veltassa™ (patiromer sorbitex calcium, RLY5016), a new molecular entity, consists of the active moiety, patiromer, and a calcium-sorbitol counterion complex. Patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the gastrointestinal tract, thus increasing fecal potassium excretion and lowering serum potassium levels. The proposed indication is for the treatment of hyperkalemia.

Veltassa ™ is supplied as a powder for suspension in water for oral administration. Veltassa™ is packaged in single-use packets containing (b) (4) 8.4, (b) (4) 16.8, (b) (4) or 25.2 grams patiromer. The proposed starting dose of Veltassa is (b) (4) 8.4 grams patiromer (b) (4) with meals, based on the serum potassium level. The dose may be increased or decreased by (b) (4) as needed, to reach the desired serum potassium range.

2.2 Tables of Currently Available Treatments for Proposed Indications

The treatment of hyperkalemia is based on the severity of hyperkalemia. For patients with severe hyperkalemia, treatment focuses on immediate stabilization of the myocardial cell membrane, rapid shifting of potassium into the intracellular space, and total body potassium elimination. For patients with moderate elevations in potassium levels and no electrocardiographic (ECG) abnormalities, a cation-exchange resin or diuretic can be used to increase excretion. Hemodialysis is also used in patients with renal failure or when pharmacologic therapy is not sufficient. These treatments for hyperkalemia are summarized in the table below.

Table 1: Currently Available Treatments for Hyperkalemia

Hyperkalemia	Treatments	Comments
Severe with ECG changes or related symptoms	Calcium iv	Ameliorates cardiac toxicity via stabilization of the myocardial cell membrane.
	Insulin+glucose infusion	Enhances potassium uptake by cells, thus decreasing the serum concentration.
	Sodium bicarbonate infusion	Used in patients with severe metabolic acidosis; raises blood pH thus shifting extracellular potassium into cells.
	Hemodialysis	For patients with renal failure and/or when the aforementioned therapies are not sufficient.
Moderate elevation with normal ECG	Diuretics	For patients who are not volume depleted with relatively preserved renal function; increases urinary potassium excretion by the kidney.
	Cation exchange resin (i.e., sodium polystyrene sulfonate)	For patients with chronic kidney disease, especially those with end stage renal disease; binds potassium in the lumen of the gastrointestinal tract, thus increasing fecal potassium excretion.

(Reviewer table)

To date, sodium polystyrene sulfonate is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. Calcium polystyrene sulfonate is marketed outside the U.S. for the same indication.

2.3 Availability of Proposed Active Ingredient in the United States

Patiromer, the active ingredient in Veltassa^{TM}, is not currently marketed in this country.

2.4 Important Safety Issues with Consideration to Related Drugs

As noted above, sodium polystyrene sulfonate is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. GI tolerability (loss of appetite, nausea, vomiting, and constipation) can be an issue for patients. According to the label, cases of intestinal necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have also been reported in association with sodium polystyrene use; the majority of these cases reported the concomitant use of sorbitol. In addition, sodium polystyrene sulfonate is not totally selective for potassium, and other cations such as magnesium and calcium can be lost during treatment, resulting in hypomagnesaemia or hypocalcemia. Because of the sodium content of the drug, the label also advises "caution" when sodium polystyrene sulfonate is administered to patients who cannot tolerate even a small increase in sodium loads (e.g., severe congestive heart failure, severe hypertension, or marked edema).

Reviewer's comment: Veltassa™ does not use sodium as a counter-ion; hence Veltassa™ would not be expected to contribute to the sodium load in patients who use the product.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The following table provides a brief overview of the pre-submission regulatory activity; major clinical issues that were discussed during these interactions are described in greater detail below the table.

Table 2: Pre-submission Activities Related to Clinical Development

Date	Activity
July 2007	Pre-IND Meeting: Agency provides comments and recommendations on the study population and issues related to study design
Dec 2007	IND submitted
March 2009	FDA advice letter: Agency provides advice on the proposed indication and the design of Study RLY5016-202
Nov 2011	End-of-Phase 2 Meeting
Feb-April 2012	Sponsor requests feedback on the design of RLY5016-301 in advance of submitting a request for special protocol assessment (SPA); Agency provides feedback
June-July 2012	Sponsor submits request for SPA for Study RLY5016-301; Agency issues no-agreement letter
Oct 2012	Agency provides advice on the revised design of Study RLY5016-301 (updated study design submitted via email by sponsor in September 2012)
Nov-Dec 2012	Sponsor resubmits request for SPA for Study RLY5016-301; Agency issues a SPA agreement letter after additional email correspondence with sponsor regarding the assay that will be used to assess for hemolysis
Feb 2013	Final statistical analysis plan (SAP) submitted for study RLY5016-301

Mar 2013	Agency provides advice on the SAP and sponsor responds
April-June 2013	Multiple communications between sponsor and Agency regarding the hemolysis assay
Sep-Oct 2013	Several communications between sponsor and Agency regarding the design of a phase 1 study (Study RLY5016-103) measuring the time to onset of the product's serum potassium lowering effect
Feb 2014	Communications between sponsor and Agency regarding the sponsor's drug-drug interaction program

(Reviewer table)

Major clinical issues that were discussed during development included:

- *Treatment* (b) (4) *claim*: At the Pre-IND meeting, the sponsor expressed interest in (b) (4) a treatment (b) (4) claim. The Agency indicated that a general claim related to the treatment of hyperkalemia would be an easier path to approval than a claim related to (b) (4) hyperkalemia (i.e., (b) (4) hyperkalemia in patients with heart failure and renal impairment who are to receive a drug or drugs that may result in elevation of serum potassium). The Agency noted that NDAs in which (b) (4) claims are sought generally require more and longer term safety data than NDAs seeking short-term treatment claims.

- (b) (4)

  In its no-agreement letter, the Division noted that there was an inherent conflict between the type of evidence needed to support the claims of treatment of hyperkalemia (b) (4) Part B of the study allows discontinuation of the RAAS inhibitor, but no down-titration. In general physicians would lower the dose of a RAAS inhibitor in response to hyperkalemia. (b) (4) would need to be based upon a study in which some down-titration (i.e., going to less than the maximum dose) of the RAAS inhibitor was allowed. Changes in the dose of the RAAS inhibitor, however, would confound the data needed to support the hyperkalemia claim. It was also noted that the dose-dependence of RAAS benefits is not well characterized, and it is not clear that enabling a higher dose of a RAAS inhibitor is a benefit. If this conflict could be resolved (perhaps via separate studies supporting the hyperkalemia (b) (4)), a description of the finding (i.e., that treatment with patiromer enabled (b) (4)

  In their second SPA request, the sponsor indicating that designing a study to achieve both goals had proved to be challenging. Therefore, the sponsor (b) (4) (b) (4)

- *Efficacy endpoints in phase 3:* The Agency indicated that the proposed primary endpoint, the mean change from baseline in serum potassium levels to week 8 in the study of Part A was acceptable, and that an earlier time point might also be reasonable. However, the Agency indicated it would also be interested in the distribution of the effect and the effect as a function of baseline potassium level. For the randomized withdrawal phase (Part B), the Agency recommended using an endpoint of change from the new baseline (beginning of the withdrawal phase) in serum potassium.

- *Dose selection:* The Division agreed with the sponsor that the optimal starting dose could be determined from one study and then confirmed in the dose-ranging study. A major issue of concern would be avoiding events of hypokalemia. Based on the phase 2 dose-ranging study, the Division indicated that the proposed starting dose and dose selection plan for the phase 3 study seemed reasonable.

- *Use of an open-label design*: Given the non-absorbed nature of RLY5016, nonclinical and clinical experience to date, and objectivity of the serum potassium endpoint, open-label studies might be acceptable.

- *Kinetics of the change in potassium*: The Agency indicated that the development program should evaluate the stability and time-course of the change in serum potassium.

- *Addressing hemolysis*: In the no-agreement letter, the Agency pointed out that methods for identifying spurious potassium levels secondary to hemolysis should be provided in the protocol to avoid false positive results of hyperkalemia and to minimize the risk of inappropriately up-titrating the dose. Later, the Division raised concern about whether Part A of the trial could serve as one of two "adequate and well controlled" trials supporting efficacy given the lack of a control arm in Part A and questions about the sensitivity of the assay used to detect hemolysis. There were several discussions between the Division and the sponsor about this issue. The Division emphasized that the effect size in Part A of the trial would need to be much larger than the upper-bound of what could be excluded by the assay if Part A was to be used to support efficacy. In the end, the sponsor provided analyses indicating that their LIH (lipemia/turbidity, icterus and hemolysis) assay had a 97.5% probability to detect a change in serum K+ > 0.36 mEq/L in samples flagged by the LIH assay as "negative" for hemolysis. The sponsor proposed a targeted mean serum K+ decrease from baseline to the end of Part A of at least 0.7 mEq/L (based on doubling the serum K+ value of 0.36 mEq/L) with a p-value of less than 0.05. The sponsor stated that they believed that this delta was sufficient to mitigate the potential impact of false negative LIH hemolysis assay results ensuring the interpretability of the serum potassium primary endpoint results for Part A, which without a placebo control group, relied on the baseline serum potassium value as the control. The Division agreed based on the low probability that hemolysis in samples flagged as "negative" could lead to potassium levels increased by as much as 0.36 mEq/L,which was small relative to the expected magnitude of the treatment effect.

- *Safety database:* There should be 6-12 months of data in at least some patients. This could be achieved in an open-label extension period. It is acceptable that most (if not all) of the long-term safety exposure data will be derived from the phase 2 study RLY5016-205 being conducted outside the US (Western and Eastern Europe), provided that the sponsor can make the case that the study findings are generalizable to medical practice in the US (e.g., study practices reflect U.S. standards of care/background therapy, etc.).

- *QT study*: A thorough QT/QTc study would not be required due to the lack of systemic exposure to this product.

- *Labeling*: The Agency indicated that the label would not likely refer to a particular potassium level. Instead, the indication would likely be for the "treatment of hyperkalemia" (as it is for sodium polystyrene sulfonate); the level of hyperkalemia requiring treatment would be left to clinicians' judgment.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In my review of the submission, I did not identify any problems or major discrepancies which might confound the efficacy and safety evaluation of this product. The quality and integrity of the data included in the submission are acceptable.

3.2 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in full compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki, informed patient consent, and Institutional Review Board approval.

Three clinical study sites were selected for audit. Two of these sites enrolled patients into the phase 3 study, Study RLY5016-301, and two enrolled patients into RLY5016-205, the applicant's phase 2 dose-range finding and long-term safety study. The sponsor site was also inspected.

Site inspections were conducted because this is an NME and most of the data were gathered at foreign sites (only 9% of subjects were enrolled from US sites in Study RLY5016-301 and no subjects were enrolled from US sites in Study RLY5016-205). Although there were sites of interest in the Ukraine (the country with the highest enrollment in Study RLY5016-301), these sites were not selected because inspections could not be conducted in the Ukraine. The three

international study sites that were selected had high enrollment rates and a larger number of responders. No single site drove the efficacy results in trial RLY5016-301 (Part A or Part B) or in trial RLY5016-205.

No significant deficiencies were observed at the sponsor site and no FDA 483 was issued. According to email correspondence from Sharon Gershon (Office of Scientific Investigations), the inspections at all investigative sites were found to be NAI and no FDA 483 was issued.

3.3 Financial Disclosures

The covered clinical studies included:

- Study RLY5016-103 titled "A Phase 1 Open-Label, Single-Arm Study of the Time to Onset of Action of RLY5016 (Patiromer) in Subjects with Chronic Kidney Disease and Hyperkalemia"
- Study RLY5016-202 titled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multiple-Dose Study to Evaluate the Effects of RLY5016 in Heart Failure Patients"
- Study RLY5016-204 titled "A Multicenter, Open-Label, Single-Arm Study to Evaluate the Feasibility of a Titration Regimen for RLY5016 in Heart Failure Patients with Chronic Kidney Disease"
- Study RLY5016-205 titled "A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone"
- Study RLY5016-301 titled "A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia"

The applicant has submitted financial disclosure information for all investigators and for the Safety Review Board (SRB) members participating in the five clinical studies listed above, with the exception of one sub-investigator (described below).

Financial disclosure information was not submitted for (b) (6) the assigned study coordinator at Site No. (b) (6) in Study (b) (6). Per the applicant, financial disclosure information was inadvertently not collected for this sub-investigator. Site No. (b) (6) screened (b) (6) subjects but did not enroll any subjects into the study; hence, the lack of disclosure information for this sub-investigator does not raise any concerns about the reliability of the data submitted in support of this application.

For all other listed investigators and SRB members, the applicant certifies that: 1) the company has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity in applicant; and 3) no listed investigator was the recipient of significant payments of other sorts. See the table below.

Table 3: Clinical Investigator Financial Disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 182		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0*		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

*The submission indicates that due diligence was made to obtain the information from the sub-investigator with missing information (see discussion above regarding (b) (6)); however the appropriate form (i.e., Form FDA 3454 with box 3 checked) was not submitted. The appropriate form will be requested from the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

RLY5016 is a powder for suspension in water for oral administration. The active ingredient is patiromer sorbitex calcium which consists of the active moiety, patiromer, a non-absorbed

potassium-binding polymer, and a calcium-sorbitol counterion (b) (4). Each gram of patiromer is equivalent to a nominal amount of 2 grams of patiromer sorbitex calcium.

The drug product of patiromer sorbitex calcium suspension includes (b) (4) % of patiromer calcium sorbitol complex and (b) (4)% of xanthan gum, (b) (4). Each packet of RLY5016 contains (b) (4) 8.4 grams, (b) (4) 16.8 grams, (b) (4) or 25.2 grams of patiromer, the active moiety. The inactive ingredient is xanthan gum.

At this time, the Quality Review is pending. Concern has been raised about (b) (4) (b) (4) could affect patient compliance, review of the clinical trial data did not raise concern (b) (4) leading to premature discontinuation of study medication.

4.2 Clinical Microbiology

This is not an antiomicrobial product.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology review has not been finalized. No adverse effects were observed in non-clinical toxicology studies and no signification absorption was seen in radiolabeled ADME studies.

Fluoride is a degradation product of RLY5016 and one potential safety concern is fluoride absorption resulting in accumulation of fluoride. According to Dr. William Link, at the maximal dose of ~50 g RLY5016, potentially (b) (4) fluoride could be released and be bioavailable. However, because of the high Ca concentration in RYL5016, it is likely that a substantial portion of the released fluoride will be in the form of CaF_2, with a (b) (4) lower solubility than sodium fluoride. Experiments in rats demonstrated that when administered at similar doses, RLY5016 (Ca) gave a (b) (4) lower fluoride Cmax and a (b) (4) lower fluoride AUC compared to RLY5016 (Na), indicating that the fluoride is (b) (4) less available in RLY5016 (Ca). According to Dr. Link, patients would likely have been symptomatic if fully exposed to the entire (b) (4) predicted fluoride dose (b) (4) and that exposure to fluoride could be a concern for children <8 years. A patient's fluoride intake in their drinking water could substantially influence their total exposure when using RLY5016.

4.4 Clinical Pharmacology

The Clinical Pharmacology review has not been finalized. A major safety concern is the potential for drug-drug interactions. Of the 28 compounds that underwent in vitro screening, seven showed > 50% binding to RLY5016 and another seven showed 30% to 50% binding. The Agency has asked the applicant to propose a pragmatic strategy to mitigate the potential risk of drug-drug interactions. The proposed strategy should be reasonably easy to implement and

should be applicable to a wide variety of medications that are commonly used in the target population and to various oral dosage forms. This issue will need to be resolved prior to approval.

4.4.1 Mechanism of Action

RLY5016 binds potassium in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels.

4.2.2 Pharmacodynamics

RLY5016 has been shown to bind potassium *in vitro*. Compared to placebo, RLY5016 doses of 12.6 grams to 50.4 grams patiromer per day resulted in dose-dependent increases in fecal potassium excretion with corresponding decreases in urinary potassium excretion and no change in serum potassium in healthy subjects. Once daily dosing of RLY5016 in healthy subjects resulted in similar changes in fecal and urinary potassium excretion compared to twice daily dosing. In hyperkalemic patients on hemodialysis, RLY5016 increased fecal potassium excretion and decreased serum potassium.

In an open-label study evaluating the onset of the potassium-lowering action of RLY5016, 25 hyperkalemic patients with CKD entered a 3-day potassium controlled diet run-in period before taking 4 fixed doses of 8.4 grams patiromer (16.8 grams/day) over a 48-hour period. From a mean baseline serum potassium of 5.93 mEq/L, statistically significant reductions were observed at 7 hours after the first dose (-0.21 mEq/L) and throughout the 48-hour dosing interval ($p \leq 0.001$). Sustained serum potassium reductions from baseline were observed for 24 hours after the last dose (Hour 34). Mean serum potassium continued to decline for 7 hours (-0.83 mEq/L at Hour 41), and at 24 hours was similar to the mean at the last dose (5.28 mEq/L at Hour 34; 5.27 mEq/L at Hour 58).

4.4.3 Pharmacokinetics

As RLY5016 is not absorbed, the pharmacokinetics of this product were not evaluated in clinical studies. Radiolabeled ADME studies were conducted in rats and dogs and both showed that patiromer was not systemically absorbed and was excreted in the feces. Quantitative whole-body autoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

5 Sources of Clinical Data

The initial NDA submission, dated October 21, 2014, served as the primary source of clinical data for this review.

5.1 Tables of Studies/Clinical Trials

The clinical development program for RLY5016 for Oral Suspension consisted of eight studies: three phase 1 studies (RLY5016-101, -102, and -103), four phase 2 studies (RLY5016-201, -202, -204, and -205) and one two-part phase 3 study (RLY5016-301) conducted under Special Protocol Assessment. As described in Section 5.2, this review focuses on five of these studies (RLY 5016-103, -202, -204, -205 and -301). The other studies (RLY 5016- 101, -102, and -201) are clinical pharmacology studies and are discussed in the clinical pharmacology review.

Table 4: Overview of Efficacy and Safety Studies

Study	Phase	Brief Study Description	Treatment Duration	Total Subjects Treated (RLY:Placebo)	Serum Potassium Status at Entry	Population	Study Design	Noted Contributions to Overall Clinical Development
Treatment Studies:								
103	Phase 1	Pharmacodynamic study	48 hours	25	Hyperkalemic	CKD	Open-label, single arm	• Time to onset of serum potassium lowering effect.
205	Phase 2	Dose-ranging study	1 year	304	Hyperkalemic	CKD[a]	Open-label, randomized, parallel arms	• Starting dose selection for Phase 3. • Efficacy and safety in the treatment of hyperkalemia for up to 1 year.
301 Part A	Phase 3	Treatment phase	4 weeks	243	Hyperkalemic	CKD	Single-blind, single arm	• 2 pivotal studies for the NDA[b]. • Part A: Efficacy and safety in the treatment of hyperkalemia, using starting doses as in the proposed labelling. • Part B: Efficacy and safety of continued treatment with RLY5016 FOS versus placebo. Confirmed efficacy observed in Part A. Demonstrated the need for continued treatment to prevent recurrence of hyperkalemia.
301 Part B	Phase 3	Randomized withdrawal phase	8 weeks	107 (55:52)	Normokalemic[c]		Single-blind, randomized, placebo-controlled, parallel arms	
Prevention Studies:								
202	Phase 2	Placebo-controlled study of fixed dosing	4 weeks	105 (56:49)	Normokalemic	Heart Failure[c]	Double-blind, randomized, placebo-controlled, parallel arms	• Efficacy and safety in the prevention of hyperkalemia. • Contributed dosing information (fixed dose). • Provided placebo-controlled efficacy data.
204	Phase 2	First study to use individualized dose titration	8 weeks	63	Normokalemic	Heart Failure and CKD	Open-label, single arm	• Efficacy and safety in the prevention of hyperkalemia. • Contributed dosing information (dose titration).

(Source: Applicant's Table 1, 2.5 Clinical Overview, page 12)

5.2 Review Strategy

The efficacy review focused on the phase 3 trial, RLY5016- 301; however, the other studies listed in the table in Section 5.1 were also reviewed for supportive evidence of efficacy.

The safety review utilized the data from all of the trials listed in the table in Section 5.1, as well as the data from the clinical pharmacology studies. Data supporting long-term safety and tolerability are provided by the applicant's one year phase 2 study, Study RLY5016-205.

5.3 Discussion of Individual Studies/Clinical Trials

The following section discusses the design of RLY5016-205, the applicant's phase 2 dose-ranging and long-term safety study, and the phase 3 trial, RLY 5016-301.

5.3.1 Study RLY5016-205

Study RLY5016-205 (also referred to as study "205" was a multicenter, randomized, open-label, dose ranging study to evaluate the efficacy and safety of RLY5016 in the treatment of hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone (AMETHYST-DN). Three-hundred and six (306) subjects were enrolled in 48 sites in 5 countries including 6 sites in Croatia, 11 sites in Georgia, 16 sites in Hungary, 7 sites in Serbia and 8 sites in Slovenia. The discussion of the protocol that follows is based on the final version of the protocol (i.e., protocol amendment 2).

Important trial dates:
Original protocol date**:** February 22, 2011
Amendment number 1: June 28, 2011
Amendment number 2: March 23, 2012
Date first subject enrolled: June 03, 2011
Date last subject follow-up visit completed: June 17, 2013

Study objectives: The primary objective of the study was to determine the optimal starting dose of RLY5016 for Oral Suspension in treating hyperkalemia in the aforementioned population. Secondary objectives were: (1) to determine the efficacy of RLY5016 in this population; (2) to determine the safety of RLY5016 in this population; and (3) to evaluate the chronic use of RLY5016.

Entry criteria:
Major inclusion criteria included:

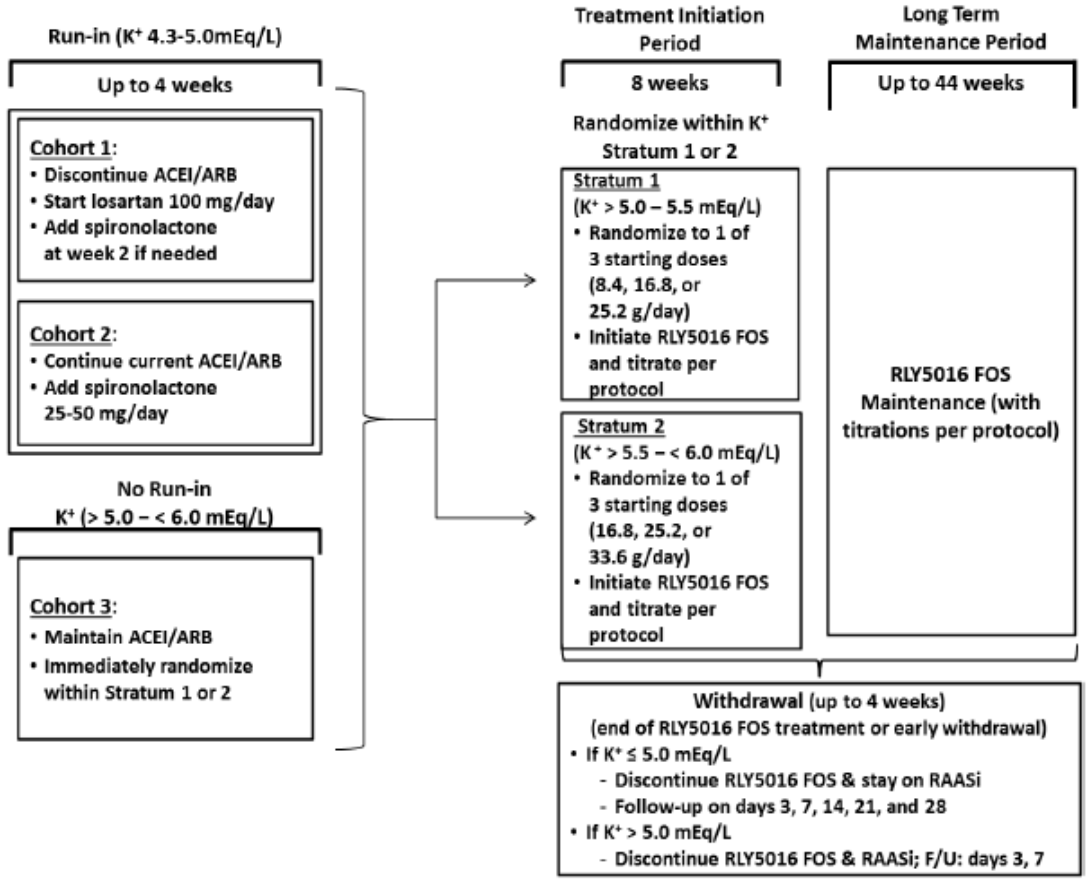
- Men and women ages 30 to 80 years old
- Serum potassium level > 5.0 to < 6.0 mEq/L at randomization
- T2DM after age 30 treated with oral medication or insulin for at least 1 year
- Chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) 15 to < 60 mL/min/1.73m^2
- ACEI and/or ARB for at least 28 days prior to screening.
- Any subject with a history of hypertension must have had an average systolic blood pressure (SBP) > 130 to ≤ 180 mmHg AND average diastolic blood pressure (DBP) > 80 to ≤ 110 mmHg (sitting). Whereas Cohorts 1 and 2 subjects must have had a diagnosis of hypertension to be enrolled in the study, subjects without a history of hypertension could be enrolledin Cohort 3.
- Urine albumin to creatinine ratio (ACR) ≥ 30 mg/g based on up to three ACR values at screening

Exclusion criteria included:

- Type 1 diabetes mellitus
- Hemoglobin A1c > 12% at screening or emergency treatment for T2DM within the last 3 months
- A confirmed systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg at any time during Screening or Run-in Period or at Baseline T0 Visit
- Central lab serum magnesium < 1.4 mg/dL (< 0.58 mmol/L) at screening (Cohort 3 subjects were evaluated based on local lab serum magnesium measurement)
- Central lab urine ACR ≥ 10000 mg/g at screening (except for Cohort 3)
- Confirmed diagnosis or history of renal artery stenosis (unilateral or bilateral)
- Diabetic gastroparesis
- Non-diabetic chronic kidney disease
- History of bowel obstruction, swallowing disorders, severe gastrointestinal disorder or major gastrointestinal surgery (e.g., large bowel resection)
- Current diagnoses of NYHA Class III or IV heart failure
- Body mass index (BMI) ≥ 40 kg/m^2
- Any of the following events having occurred within 2 months prior to screening: unstable angina, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, transient ischemic attack, or stroke, use of an intravenous cardiac medication
- Prior kidney transplant, or anticipated need for transplant during study participation
- Active cancer, currently on cancer treatment or history of cancer in the past 2 years except for nonmelanocytic skin cancer which is considered cured
- History of alcoholism or drug/chemical abuse within 1 year
- Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) > 3 times the upper limit of normal
- Loop and thiazide diuretics or other antihypertensive medications (calcium channel blocker, beta-blocker, alpha blocker, or centrally acting agent) that had not been stable for at least 28 days prior to screening or was not anticipated to remain stable during study participation
- Current use of polymer-based drugs (e.g., sevelamer, sodium polystyrene sulfonate, colesevelam, colestipol, cholestyramine), phosphate binders (e.g., lanthanum carbonate), or other potassium binders, or their anticipated need during study participation
- Current use of lithium, potassium sparing medications including aldosterone antagonists (e.g., spironolactone), drospirenone, potassium supplements, bicarbonate, or baking soda in the last 7 days prior to screening

Study Design: A schematic of the study design is shown below. In brief, the study had a run-in period, a Treatment Initiation Period (TIP) that lasted 8 weeks, a Long-term Maintenance Period (LTMP) that lasted 44 weeks, and a withdrawal period of up to 4 weeks. As shown in the figure below, the trial population was divided into three cohorts. During the Run-in Period, Cohort 1 subjects discontinued pre-study RAASi medication and started losartan 100 mg. Spironolactone was added when needed for additional blood pressure control. Cohort 2 subjects continued on their pre-study ACEI or ARB medication and added spironolactone to the regimen. Eligible subjects with hyperkalemia (serum potassium > 5.0 to < 6.0 mEq/L) at screening or start of the Run-in Period entered the TIP immediately while continuing to receive their current ACEI and/or ARB regimen (Cohort 3).

Figure 1: Design of Study RLY5016-205



(Applicant's figure from CSR 205, figure 1, page 41)

Run-in Period: Subjects who were hyperkalemic (serum potassium > 5.0 and < 6.0 mEq/L) at the Screening visit or at the first Run-in Period visit were randomly assigned to RLY5016 immediately. Subjects who were not hyperkalemic at screening AND at the first Run-in Period visit entered into a Run-in Period of up to 4 weeks intended to allow investigators to initiate RAAS therapy, or to continue the subject's current RAAS therapy with an ACEI and/or ARB, along with an aldosterone antagonist to provide additional proteinuria reduction and hypertension control. Upon development of hyperkalemia during the Run-in Period, subjects entered the treatment initiation period. Subjects who entered the treatment initiation period were assigned to one of two strata according to their baseline serum potassium level and initiated RLY5016 at randomly assigned starting doses in a 1:1 ratio.

Treatment Period: During the treatment period, the starting dose of RLY5016 could be titrated up or down, starting on Day 3 and up to the Week 51 visit.

Withdrawal Period: In order to assess the effect of the withdrawal of RLY5016 on serum potassium when receiving treatment with RAAS inhibitors, normokalemic subjects (serum

potassium ≤ 5.0 mEq/L) at the end of treatment visit remained on all RAAS inhibitors for 28 days after discontinuation of RLY5016, returning for five follow-up visits. Subjects who experienced significant hyperkalemia during the follow-up period were treated per standard of care (as judged by the investigator). Subjects with serum potassium > 5.0 mEq/L at the end-of-treatment visit discontinued RLY5016, all RAAS inhibitors, and returned for two follow-up visits on follow-up days 3 and 7.

Dosing regimen: The starting doses for the two statum are shown in the table below.

Table 5: Stratum and RLY5016 Starting Dose Assignments

Stratum 1 (Serum Potassium > 5.0 to 5.5 mEq/L)		Stratum 2 (Serum Potassium > 5.5 to < 6.0 mEq/L)	
RLY5016 (dose expressed as calcium form of the polymer)	RLY5016 FOS (dose expressed as anion form [active moiety] of the polymer [patiromer])[a]	RLY5016 (dose expressed as calcium form of the polymer)	RLY5016 FOS (dose expressed as anion form [active moiety] of the polymer [patiromer])[a]
10 g/day	8.4 g/day	20 g/day[b]	16.8 g/day[b]
20 g/day	16.8 g/day	30 g/day	25.2 g/day
30 g/day	25.2 g/day	40 g/day	33.6 g/day

(Source: Applicant's Table 2, CSR, page 38)

a. The description of the dose of RLY5016 for Oral Suspension changed during the course of its clinical development. b. The 20 g/day (16.8 g/day patiromer) dose for Stratum 2 was added in Protocol Amendment 1, and thus randomization to starting doses in both Stratum 1 and Stratum 2 was in a 1:1:1 ratio after the amendment.

As previously noted, during the treatment period, the starting dose of RLY5016 could be titrated up or down, starting on Day 3 and up to the Week 51 visit to maintain serum potassium in the target range of 4.0–5.0 mEq/L. The titration algorithm was as follows:

- If the local laboratory serum potassium value was within the **4.0–5.0 mEq/L** range, no titration of RLY5016 was required and the subject continued the same RLY5016 dose until the next scheduled study visit.
- If the serum potassium was **> 5.5 to < 6.2 mEq/L** and the serum potassium had decreased by ≥ 0.4 mEq/L from the previous scheduled visit, the RLY5016 dose was increase by 10 g/d (except for subjects already on the maximum dose of 60 g/d, who were to be withdrawn from the study).
- If the serum potassium was **> 5.5 to < 6.2 mEq/L** and the serum potassium had decreased by <0.4 mEq/L from the previous scheduled visit, the RLY5016 dose was increased by 10 g/d (except for subjects already on the maximum dose of 60 g/d, who were to be withdrawn from the study). The subject was to return for a visit 1, 2, or 3 days later (timing at the Investigator's discretion). At this return visit, if the serum potassium had decreased by ≥ 0.4 mEq/L from the previous visit, there was no change in the RLY5016 dose and the subject was to return for the next scheduled study visit. If the serum potassium < 0.4 mEq/L, the subject must be withdrawn from the study.
- If the serum potassium was **> 5.0 to 5.5 mEq/L** and the serum potassium had decreased by ≥ 0.4 mEq/L from the previous scheduled visit, there was no change in the RLY5016 dose.
- If the serum potassium was **> 5.0 to 5.5 mEq/L** and the serum potassium had decreased by < 0.4 mEq/L from the previous scheduled visit, the RLY5016 dose was increased by

10 g/d (except for subjects already on the maximum dose of 60 g/d, who were to be withdrawn from the study).

- If the serum potassium was **3.5 to < 4.0 mEq/L**, the RLY5016 dose was decreased by 10 g/d (except for subjects already on the minimum dose of 0 g/d, who were to be withdrawn from the study).
- If the serum potassium was **< 3.5 mEq/L**, the RLY5016 dose was decreased to 10 g/d or to 0 g/d (if the subject was currently on 10 g/d). The patients who are already on the minimum dose of 0 g/d must be withdrawn from the study).

Subject withdrawal: Subjects who met any of the following criteria were withdrawn from the study and treated as per standard of care by the investigator:

- Had an ECG change related to hyper- or hypokalemia (e.g., ventricular arrhythmias, peaked T waves or increased U waves)
- Had eGFR decrease to < 10 mL/min/1.73 m^2 or need for dialysis
- Had symptomatic hypotension or SBP < 110 mmHg (with or without symptoms) that persisted after dose of spironolactone had been reduced and/or other non-RAAS inhibitor agents had either been removed or doses had been decreased
- Had confirmed hypertension with either SBP > 180 mmHg or DBP > 110 mmHg (repeated 30 minutes after the initial readings) at any time during the study if the subject was on at least three antihypertensive agents
- Had serum magnesium < 1.0 mg/dL (< 0.42 mmol/L)
- Had urine ACR ≥ 10,000 mg/g
- Experienced a treatment-related SAE
- Became pregnant
- High serum potassium defined as: ≥ 6.0 mEq/L during the Run-in Period (R1, R2, R3) or at the baseline visit (T0) or ≥ 6.2 mEq/L during the TIP, or ≥ 6.5 mEq/L during the LTMP
- Low serum potassium defined as: < 3.5 mEq/L during the Treatment Initiation Period or < 3.5 mEq/L during the Long Term Maintenanc Period and were already on the minimum dose of RLY5016

Sample size determination: Each stratum was to have approximately 150 subjects randomized in a 1:1:1 allocation ratio (50 subjects per dose group) to ensure that at least 126 subjects (42 subjects per dose group) had received investigational product and could contribute primary efficacy data assuming a 15% non-evaluable rate. The sample size of 42 subjects per dose group was based on an effect size of 0.5 for the primary efficacy measurement, the change in serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration. The sample size was estimated to have 90% power to detect a statistically significant change at a significance level of 0.05 within each dose group. The calculation was based on a two-sided one-sample paired t-test, and a significance level of $\alpha = 0.05$.

Efficacy analysis: The primary efficacy parameter was the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration (if before week 4).

The major secondary efficacy parameters in the treatment initation phase included the following:

- Mean change in serum potassium from baseline to week 8 or prior to the initiation of RLY5016 dose titration
- Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8
- Mean change in serum potassium from baseline to post-baseline visits
- Mean change in serum potassium from end of RLY5016 treatment to follow up visits
- Proportion of patients requiring RLY5016 titration
- Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of week 8

The major efficacy parameters for the Long-Term Maintenance Period included the following:

- The interpolated time serum potassium concentrations stay within the target range of 3.8 to 5.0 mEq/L over the duration of the Long-Term Maintenance Period of the trial
- Proportion of patients with serum potassium values below, within, and above various ranges by visit
- Mean change in serum potassium from baseline (T0) to post-baseline visits
- Mean change in serum potassium from end of RLY5016 treatment to follow up visits
- Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria
- RLY5016 doses by visit
- Number and type of RLY5016 titrations by visit (type 1 error rate was not controlled)

Interim data analysis: A pre-specified interim data analysis was performed for this study based on data collected from approximately 120 subjects (approximately 20 subjects per starting dose group) who completed the Week 4 treatment visit or who had prematurely discontinued from the study and had primary efficacy data. These interim results were used to determine the optimal starting dose of RLY5016 for each serum potassium stratum for future studies.

5.3.2 Study RLY5016-301

Study RLY5016-301 was a two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalemia. The study was conducted under Special Protocol Assessment. Two hundred forty-three (243) subjects were enrolled in 71 sites in 10 countries including Croatia, Czech Republic, Denmark, Georgia, Hungary, Italy, Serbia, Slovenia, Ukraine, and United States. The discussion of the protocol that follows is based on the final version of the protocol (i.e., protocol amendment 1).

Important trial dates:
Original protocol date**:** November 9, 2012
Amendment number 1: February 1, 2013
Date first subject enrolled: February 20, 2013
Date last subject completed: August 6, 2013

Study objectives: The objectives of Part A were to evaluate the efficacy and safety of RLY5016 for Oral Suspension for the treatment of hyperkalemia. The objectives of Part B were to evaluate the effect of withdrawing RLY5016 for Oral Suspension on serum potassium control, to assess whether chronic treatment with RLY5016 for Oral Suspension prevents the recurrence of hyperkalemia and to provide placebo-controlled safety data.

Entry criteria:
Part A- Major inclusion criteria**:**
- Age 18 – 80 years old at screening
- Serum potassium: local laboratory serum potassium level that was 5.1 to < 6.5 mEq/L at screening
- Other inclusion criteria were similar to those in Study RLY5016-205

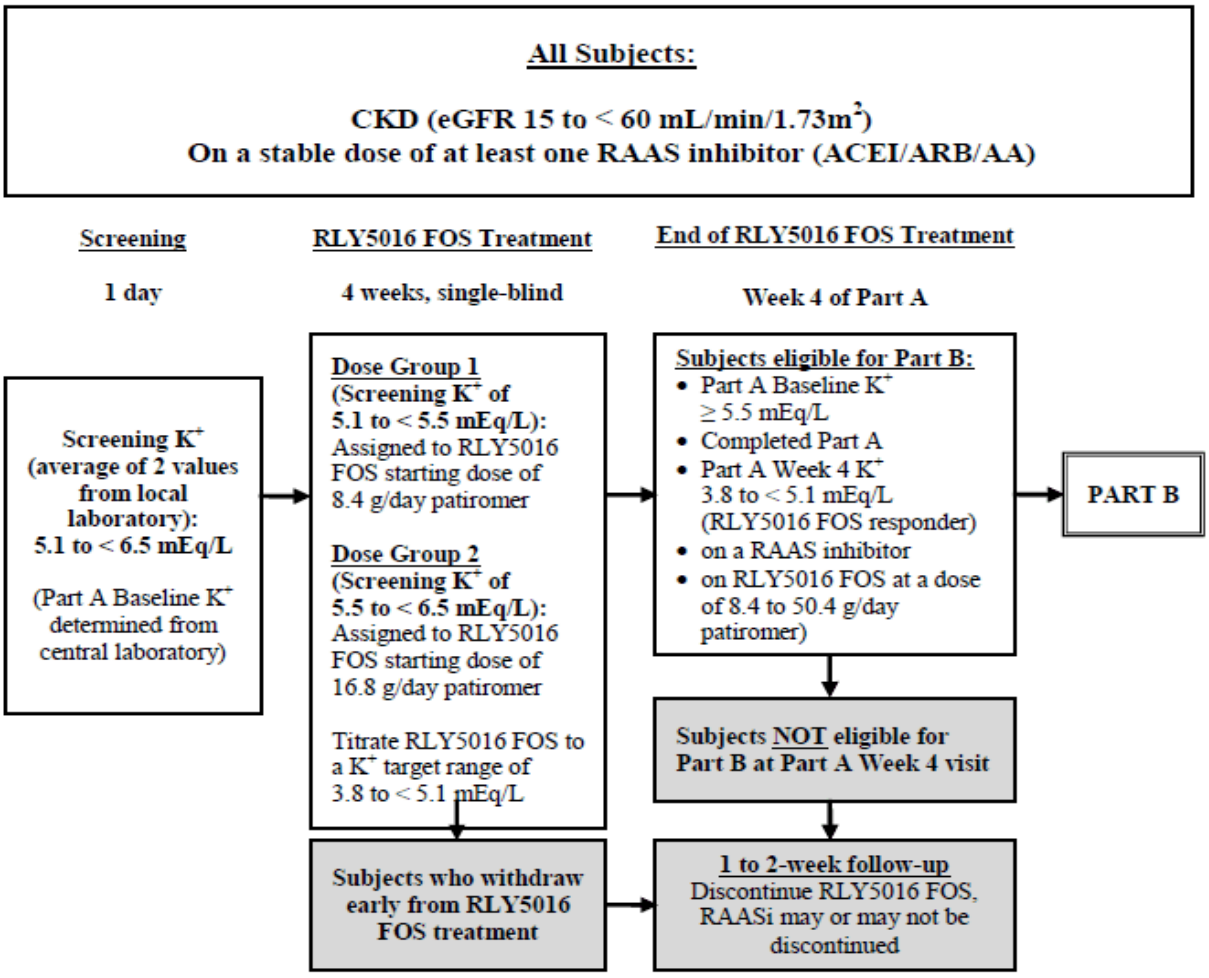
Part A- Major exclusion criteria**:**
- A HbA1c measurement of > 10.0% within the previous 6 months in subjects with T2DM
- Anuria or history of acute renal insufficiency in the past 3 months
- New York Heart Association Class IV heart failure
- Other criteria were similar to those in Study RLY5016-205

Part B- Inclusion criteria:
- Baseline serum potassium (central laboratory) at the beginning of Part A ≥ 5.5 mEq/L
- Completed the 4 weeks of dosing with RLY5016 in Part A
- Serum potassium (local laboratory) at the Part A Week 4 visit in target range for Part A (≥ 3.8 mEq/L and < 5.1 mEq/L)
- Receiving RLY5016 at a dose of 8.4 g/day to 50.4 g/day patiromer at the Part A Week 4 visit
- Still receiving treatment with a RAASi at the Part A Week 4 visit

Part B-Exclusion criteria:
- Part A baseline central laboratory serum K+ < 5.5 mEq/L
- Did not complete Part A, the Patiromer Treatment Period
- Local laboratory measured serum K+ value at the Part A Week 4 Visit (AW4) outside of the target range, either < 3.8 or ≥ 5.1 mEq/L.
- Not receiving treatment with a RAAS inhibitor medication at the Part A Week 4 Visit (AW4)

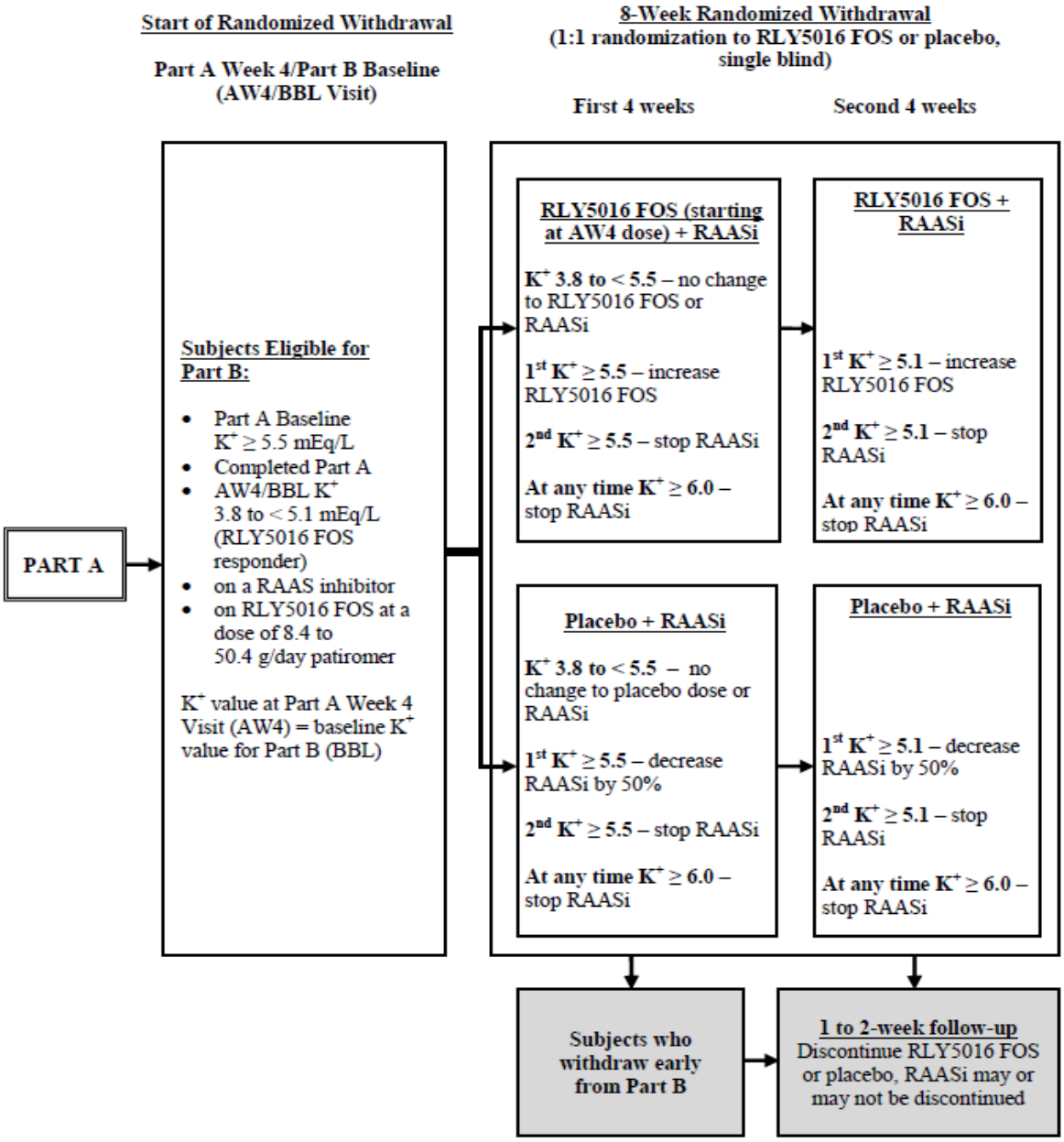
Study design: As shown in the figure below, the study consisted of two sequential parts. Part A was an assessment of 4 weeks of dosing with RLY5016 in the treatment of hyperkalemia. Part B was a randomized, placebo-controlled, 8-week assessment of the withdrawal of RLY5016 in subjects with a baseline serum potassium (central laboratory) at the beginning of Part A ≥ 5.5 mEq/L who responded (defined later) to 4 weeks of treatment with RLY5016 during Part A. Approximately 240 subjects were to be enrolled in Part A and at least 80 subjects were to be randomized into Part B of the study.

Figure 2: Schematic of Part A of Study RLY5016-301



RLY5016 FOS = RLY5016 for Oral Suspension
(Source: Applicant's Figure 1, CSR 301, page 54)

Figure 3: Schematic of Part B of Study RLY5016- 301



AW4 = Part A Week 4 visit; BBL = Part B Baseline visit; RLY5016 FOS = RLY5016 for Oral Suspension
(Source: Applicant's Figure 2, CSR 301, page 57)

Part A –Treatment Phase: Subjects who met eligibility criteria were assigned to one of two RLY5016 starting dose groups:

- Dose Group 1 – Subjects with a Part A screening serum potassium (local laboratory) of 5.1 to < 5.5 mEq/L were assigned to a starting RLY5016 for Oral Suspension dose of 8.4 g/day patiromer (administered as 4.2 g twice daily [BID]).

- Dose Group 2 – Subjects with a Part A screening serum potassium (local laboratory) of 5.5 to < 6.5 mEq/L were assigned to a starting RLY5016 for Oral Suspension dose of 16.8 g/day patiromer (administered as 8.4 g BID).

The dose of RLY5016 was titrated, if needed, based on the serum potassium level, assessed starting at the Part A Day 3 visit and continuing through weekly visits (Part A Week 1, 2 and 3) to the end of 4 weeks of treatment with the aim of achieving a serum potassium in the target range (Part A target range: 3.8 to < 5.1 mEq/L). If a subject's serum potassium level (local laboratory) was outside of this target range, dose titration was performed according to a protocol specified Part A titration algorithm. The dose could be titrated to a minimum of 0 g/day patiromer and a maximum of 50.4 g/day patiromer; the Part A titration algorithm generally specified dose changes in increments of ±8.4 g/day patiromer, but allowed an option for a larger decrease, including a decrease to 0 g/day or an increase to 50.4 g/day, if indicated. The titration algorithm also specified discontinuation of the RAASi dose (1) if the serum potassium level was ≥ 6.5 mEq/L or (2) if the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of RLY5016 for Oral Suspension (50.4 g/day patiromer). Depending on the serum potassium level, the titration algorithm specified mandatory safety visits within 24 or 72 hours.

Assessments at all scheduled visits during Part A included serum potassium (both local laboratory and central laboratory), serum chemistry (including serum creatinine and eGFR), plasma renin activity and serum aldosterone, 12-lead electrocardiograms (ECGs), vital signs and assessments of adverse events (AEs) and concomitant medications.

Subjects who withdrew early from the study during the 4 weeks of Part A or who, at the end of Part A, were not eligible for Part B, entered a 1 to 2-week follow-up period to Part A during which RLY5016 for Oral Suspension was not administered and serum potassium was monitored. Part A follow-up visits were scheduled at 3 and 7 days after stopping treatment. Depending on the serum potassium level, an additional Part A follow-up visit at 14 days after stopping was required. Part A follow-up included the possibility of dose reduction or discontinuation of RAASi and the specification of standard care for hyperkalemia if indicated based on the serum potassium level.

Part B –Withdrawal Phase: Part B was a randomized, placebo-controlled, 8-week assessment of the withdrawal of RLY5016. Subjects with a baseline serum potassium ≥ 5.5 mEq/L (central laboratory) at the beginning of Part A were entered into Part B of the study if they had responded to the 4 weeks of treatment with RLY5016 during Part A, defined as completing Part A and satisfying all of the following at the Part A Week 4 visit: (1) serum potassium (local laboratory) in the target range for Part A (3.8 to < 5.1 mEq/L), (2) receiving a RAASi and (3) receiving RLY5016 at a dose of 8.4 to 50.4 g/day patiromer.

Subjects eligible for Part B were randomized equally to (1) continue RLY5016 at the same daily dose as administered at the time of the Part A Week 4 visit OR (2) discontinue RLY5016 and receive placebo for an additional 8 weeks. At the beginning of Part B, a subject's dose of RAASi was the same as had been administered at the time of the Part A Week 4 visit. During Part B,

RLY5016 and RAASi dose modification or discontinuation were performed according to protocol-specified titration algorithms based on serum potassium (local laboratory) levels assessed starting at the Part B Day 3 visit and continuing through weekly visits (Part B Week 1, 2, 3, 4, 5, 6 and 7) to the end of the 8 weeks of the RLY5016 withdrawal phase.

Because the primary efficacy endpoint for Part B was determined during the first 4 weeks of Part B, the titration algorithm specified no change of dose or discontinuation of RLY5016/placebo or RAASi during the first 4 weeks of Part B unless the serum potassium level was < 3.8 mEq/L or ≥5.5 mEq/L. If a subject's serum potassium was < 3.8 mEq/L, the subject discontinued RLY5016 /placebo, was withdrawn early from Part B and entered a follow-up period to Part B. To help retain subjects for the collection of 8 weeks of placebo-controlled safety data, an intervention (increase in RLY5016 dose or, for subjects receiving placebo, decrease in RAASi dose) was specified during the first 4 weeks of Part B if a subject's serum potassium was ≥ 5.5 mEq/L. After the first 4 weeks of Part B, the titration algorithm also specified an increase in RLY5016 dose upon the initial occurrence of a serum potassium ≥ 5.1 mEq/L. During Part B, the RLY5016 dose could be increased to a maximum of 50.4 g/day patiromer in increments of 8.4 g/day patiromer. Depending on the serum potassium level, the Part B titration algorithms also specified mandatory safety visits within 24 or 72 hours and/or early withdrawal from Part B of the study.

Subjects who either withdrew early from or completed the Part B 8-week RLY5016 withdrawal phase entered a 1- to 2-week follow-up period to Part B during which neither RLY5016 nor placebo was administered, and serum potassium was monitored. Part B follow-up visits were scheduled at 3 and 7 days after stopping RLY5016/placebo. Depending on the serum potassium level, an additional Part B follow-up visit at 14 days after stopping RLY5016/placebo was required. Part B follow up included the possibility of dose reduction or discontinuation of RAASi and the specification of standard care for hyperkalemia if indicated based on the serum potassium level.

Assessments at all scheduled visits during Part B were the same as in Part A.

Measures taken to address hemolysis: Because hemolysis of blood specimens could result in spuriously high potassium levels, leading to inappropriate up-titrating of the investigational product and causing difficulties in interpreting the efficacy analyses, the Laboratory Manual included a detailed description of the recommended phlebotomy, sample preparation and transportation procedures to minimize hemolysis.

If a central laboratory blood sample was identified as hemolyzed by site personnel before it was sent to the central laboratory, a repeat blood draw was performed if possible (e.g., if the subject was still at the site) and the resulting serum sample was sent to the central laboratory for analysis in place of the hemolyzed sample.

Upon receipt of each blood sample for potassium analysis, the central laboratory was to perform a validated, semi-quantitative test to assess for evidence of hemolysis by measuring levels of free hemoglobin in serum using a lipemia, icterus, hemolysis (LIH) assay. For any sample determined

by the LIH assay to be positive for hemolysis, the serum potassium result was to be excluded from the central laboratory database and the corresponding potassium value for that visit was to be handled in the statistical analysis as a missing central laboratory serum potassium value. In addition, for any samples with an unusually high serum potassium level (e.g., 11.0 mEq/L), the central laboratory was to exclude the potassium result from the central laboratory database (even if the LIH assay did not suggest hemolysis) and the potassium value was to be handled in the statistical analysis as missing.

If a blood sample taken for local laboratory analysis of serum potassium level (used for titration and subject management) was identified as hemolyzed, the site repeated the serum potassium measurement from a separate blood draw, if possible. This allowed accurate decision-making regarding titration of RLY5016 and continuation or discontinuation of RAASi therapy.

Sample size determination:
Part A: The sample size in Part A was driven by the plan to have at least 90% statistical power for the primary endpoint in Part B, which required 80 subjects. Thus, Part A was to enroll approximately 240 subjects in order to have approximately 80 responders enroll into Part B. With 240 subjects enrolled, Part A would have more than 99% power to detect a mean change from baseline in serum potassium of at least 0.3 mEq/L. This calculation was based on a two-sided one sample paired t-test, significance level of $\alpha = 0.05$, and the assumption of a standard deviation of 0.55.

Part B: Part B was to enroll subjects from Part A with a locally measured serum potassium level of 3.8 to < 5.1 mEq/L at Part A Week 4 Visit (AW4), which would become the Part B Baseline Visit (BBL) for the subjects who qualified for Part B treatment Phase. The required sample size for Part B was based on the assumption of a mean difference of 0.5 mEq/L in change of K+ between the placebo and RLY5016 groups; a standard deviation of change of 0.55; and the assumption that the treatment groups would be compared using Hodges-Lehmann test of the median difference in changes. A sample size of 40 in each group gave over 90% power to test the difference between the median changes at a two-sided type I error rate of 0.05.

Efficacy analysis:
Part A: The primary efficacy outcome in Part A was the change in serum potassium from Part A Baseline to Part A Week 4. The mean change would be estimated using a longitudinal repeated measures model that includes two binary covariate for the presence of HF at baseline (yes/no) and T2DM at baseline (yes/no) and a continuous covariate containing the Baseline Part A level of serum K+. The estimated mean change and its 95% confidence interval would be calculated from the model. For each person, the model would use all centrally measured values of serum potassium from Week 1 through the Week 4 Visit. In addition, parameters from the model would be used to describe the average potassium over the 4 week period (i.e., area under the curve). Part A had a single secondary efficacy outcome: having a serum K+ level in the target range of 3.8 to < 5.1 mEq/L at Week 4. The proportion in range would be formally estimated only if the 95% confidence interval for the primary outcome did not include 0. The denominator would consist of all subjects enrolled in Part A who received at least one dose of RLY5016.

Part B: The primary efficacy outcome in Part B was the change in serum potassium from Part B Baseline (Part A Week 4) to one of the two following conditions:

- Part B Week 4, for subjects whose local serum K+ remains in the range of 3.8 to < 5.5 mEq/L up to Week 4; or
- An earlier time point when the subject first has a local serum K+ <3.8 mEq/L or ≥ 5.5 mEq/L.

An analysis of covariance (ANCOVA) model with strata used at randomization would be used to compare the treatment groups and estimate a mean difference in ranks. To compare RLY5016 with placebo, the difference between the mean ranks would be tested using a t-test. The type I error rate would be 0.05, two-sided. A Hodges-Lehmann estimate, along with its 95% confidence interval, would be used to calculate the difference between the RLY5016 and placebo groups in median change in serum potassium. The study had the following two secondary outcomes which would be tested formally only if the primary outcome was statistically significant:
1. Having K+ ≥ 5.1 mEq/L at any time through Week 8
2. Having K+ ≥ 5.5 mEq/L at any time through Week 8

Reviewer comments: The Division agreed with the applicant that Part A and Part B in Study RLY5016-301 could be viewed as separate efficacy studies and that together, both parts could provide the efficacy data needed to support a marketing application.

6 Review of Efficacy

Primary support for efficacy for the treatment of hyperkalemia is provided by Study 301, a two-part (Part A and Part B), single-blind, phase 3 study in patients with hyperkalemia. Each part of the study can be viewed as a "pivotal" efficacy trial. Data from 4 other clinical studies, including a dose ranging study (Study 205), Study 103, Study 202 and Study 204, also provide support for efficacy.

The primary efficacy endpoint for Part A of Study 301 was the change in serum potassium from the Part A Baseline to the Part A Week 4 visit; the mean change was estimated using a longitudinal repeated measures model. The mean change in serum potassium from the Part A Baseline to Part A Week 4 was -1.01 mEq/L [95% CI: (-1.07, -0.95); p < 0.001). The primary efficacy endpoint for Part B of Study 301 was the change from the Part B Baseline serum potassium to either the Part B Week 4 visit, if the subject's serum potassium remained ≥ 3.8 mEq/L and < 5.5 mEq/L up to the Part B Week 4 visit, or the earliest Part B visit at which the subject's serum potassium was < 3.8 mEq/L or ≥ 5.5 mEq/L. The estimated difference in the median change from the Part B baseline (placebo minus RLY5016) was 0.72 mEq/L (95% CI of 0.46 to 0.99; p<0.001 for between-group difference in mean ranks of change). Therefore, the Part A and Part B primary efficacy endpoints were met.

In both Part A of Study 301 and Study 205, reductions of mean serum potassium from baseline to Week 4 were similar in subjects with initial serum potassium > 5.0 to < 5.5 mEq/L (mild hyperkalemia) and in those with initial serum potassium of ≥ 5.5 to < 6.5 mEq/L (moderate to

severe hyperkalemia) across all dose groups. Statistically significant mean reductions were also observed at every post baseline time point in subjects receiving RLY5016 through Week 12 in studies 301 and 205. Beyond Week 12 in Study 205, mean serum potassium was decreased from baseline at all time points through to Week 52.

Other studies, such as Study 202, also provide support for efficacy. In Study 202, which evaluated RLY5016 for the prevention of hyperkalemia in subjects with heart failure (HF) with or without CKD, the change from baseline in serum potassium to the end of the 28-day treatment period was significantly lower in the RLY5016 treatment group as compared with the placebo group. The proportion of subjects who experienced hyperkalemia (defined as a serum potassium level > 5.5 mEq/L) at any time during the 28-day treatment period was also statistically significantly lower in the RLY5016 group than in the placebo group.

Most of the subjects enrolled in the phase 3 trial were enrolled at sites outside the U.S.; however, subjects had conditions that would be expected to predispose patients to the development of hyperkalemia in the U.S. (i.e., CKD, HF, diabetes, and use of a RAASi), and hence the findings are relevant to patients in the U.S. In addition, in subgroup analyses, the efficacy of RLY5016 was preserved across age groups, gender, CKD stage, and HF status (with or without HF). Although the clinical development program included very few non-Caucasian subjects, given the mechanism of action of RLY5016, efficacy is not expected to be affected by race.

In the applicant's proposed label, the recommended starting doses are 8.4 g patiromer QD for patients presenting with a serum potassium (b) (4) The proposed regimen is different from the regimen used in the clinical studies; in the pivotal efficacy study, a BID dosing regimen was used. However a QD regimen is likely to mitigate the risk of a drug-drug interaction, and, according to the clinical pharmacology reviewer, should provide acceptable efficacy in lowering serum potassium levels. The aforementioned daily starting doses, followed by titration for effect, produced statistically significant reductions in serum potassium and resulted in the majority of subjects reaching, and remaining in, the target serum potassium range. The overall titration burden was low, with most of the subjects requiring 0 or 1 dose adjustment during the first 4 weeks of treatment. Also, this dosing regimen was associated with a low risk of hypokalemia. At this time, the clinical pharmacology reviewer does not believe a different starting dose is needed in subjects with higher baseline potassium levels and the label should be revised to reflect the final conclusions of the Office of Pharmacology.

In summary, in the pivotal study and other supportive efficacy studies, RLY5016 was effective in lowering potassium levels and enabled the majority of subjects to reach and/or remain in the target range (i.e., normal level of potassium). The ability to titrate RLY5016 provides the prescribing clinician flexibility to individualize dosing to achieve larger or smaller potassium reductions in response to changes in the patient's serum potassium levels and underlying clinical state. The time of onset of action (~7 hours) limits the utility of this therapy in settings where potassium must be acutely lowered.

6.1 Indication

The proposed indication for VELTASSA™ (patiromer, RLY5016) is for the treatment of hyperkalemia.

6.1.1 Methods

The efficacy evaluation focused on the pivotal study, Study RLY5016-301, a two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalemia. Each part of this study can be viewed as a "pivotal" study supporting efficacy. A detailed discusson of the results of Study RLY5016-301 is provided in this section. In addition, the following four studies, which also provide data to support efficacy, are discussed in this section.

- RLY5016-205 - "A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARBs Drugs, with or without Spironolactone."
- RLY5016-103 - "A Phase 1 Open-Label, Single Arm Study of the Time to Onset of Action of RLY5016 (Patiromer) in Subjects with Chronic Kidney Disease and Hyperkalemia."
- RLY5016-202 - "A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose Study to Evaluate the Effects of RLY5016 in Heart Failure Patients."
- RLY5016-204 - "A Multicenter, Open-Label, Single-Arm Study to Evaluate a Titration Regimen for RLY5016 in Heart Failure Patients with Chronic Kidney Disease.

6.1.2 Demographics

The following discussion focuses on demographics in Parts A and B of the pivotal trial.

Demographics in Part A of Study RLY5016-301: Of the 243 subjects enrolled into Part A, 58% were male and 98% were Caucasian; the median age was 65 years (range: 29 to 80 years). Ninety-two patients had a serum potassium in the range of 5.1 to 5.5 mEq/L at screening and were assigned to Dose Group 1 (starting dose of 8.4 g/day patiromer). A total of 151 subjects had a serum potassium in the range of 5.5 to 6.5 mEq/L at screening and were assigned to Dose Group 2 (starting dose of 16.8 g/day patiromer).

The distribution of gender and age was similar in the two starting dose groups. Based on the screening serum creatinine result measured by the central laboratory and the CKD-EPI equation, 45% (109/243) of the subjects had Stage 4 CKD or worse (eGFR < 30 mL/min/1.73 m^2), 26% (63/243) had Stage 3b CKD (eGFR 30 to < 45 mL/min/1.73 m^2), 20% (49/243) had Stage 3a CKD (eGFR 45 to < 60 mL/min/1.73 m^2), and 9% (22/243) had Stage 2 CKD (eGFR 60 to < 90 mL/min/1.73 m^2). Approximately 57% of subjects had type 2 DM, 42% had heart failure and 97% had hypertension. These data are summarized in the tables below.

Table 6: Demographics (Part A ITT Population)

Demographic Characteristic	Dose Group 1 5.1 to < 5.5 mEq/L N = 92	Dose Group 2 5.5 to < 6.5 mEq/L N = 151	Total 5.1 to < 6.5 mEq/L N = 243
Sex, n (%)			
Male	49 (53)	91 (60)	140 (58)
Female	43 (47)	60 (40)	103 (42)
Age at informed consent (years)			
n	92	151	243
Mean (SD)	64.6 (11.0)	63.9 (10.2)	64.2 (10.5)
Range (min, max)	32, 80	29, 80	29, 80
Quartiles (25th, median, 75th)	60, 66, 73	59, 65, 72	60, 65, 72
Age category, n (%)			
<65 years of age	39 (42)	73 (48)	112 (46)
≥65 years of age	53 (58)	78 (52)	131 (54)
≥75 years of age	16 (17)	25 (17)	41 (17)
Race, n (%)			
White	88 (96)	151 (100)	239 (98)
Black or African American	3 (3)	0	3 (1)
American Indian or Alaska Native	1 (1)	0	1 (< 1)
Ethnicity, n (%)			
Not Hispanic or Latino	88 (96)	148 (98)	236 (97)
Hispanic or Latino	4 (4)	3 (2)	7 (3)

(Applicant's table from CSR 301 table 21, page 136)

Table 7: Part A Baseline Medical History (Part A ITT Population)

Medical condition		Dose group 1 (5.1 to <5.5 mEq/L) N=92	Dose group 2 (5.5 to <6.5 mEq/L) N=151	Total (5.1 to <6.5 mEq/L) N=243
Chronic Kidney Disease	Stage 2	6 (7%)	16 (11%)	22 (9%)
	Stage 3a	22 (24%)	27 (18%)	49 (20%)
	Stage 3b	24 (26%)	39 (26%)	63 (26%)
	Stage 4 or worse	40 (43%)	69 (46%)	109 (45%)
Type II diabetes		52 (57%)	87 (58%)	139 (57%)
Heart Failure		39 (42%)	63 (42%)	102 (42%)
Prior myocardial infarction		19 (21%)	41 (27%)	60 (25%)
Hypertension		90 (98%)	146 (97%)	236 (97%)

(Reviewer's table)

Baseline medications of interest in Part A are summarized in the table below. For study eligibility, subjects were required to have been on a stable dose of at least one RAASi (ACEI, ARB or AA) for at least 28 days prior to and at the time of screening. At the Part A baseline, 17% (41/243) of subjects were receiving dual RAASi blockade (defined as any combination of at least two of the following: ACEI, ARB, AA or renin inhibitor). Forty-four percent (106/243) of subjects were considered to be on a "maximal RAASi medication dose" as determined by the investigator (a question on the eCRF asked the investigator whether the subject was on a maximal RAASi medication dose).

Table 8: Part A Baseline Concomitant Medication Use (Part A ITT Population)

Medication Class	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 (%)
RAASi	**92 (100)**	**151 (100)**	**243 (100)**
Angiotensin-converting-enzyme inhibitor	68 (74)	102 (68)	170 (70)
Angiotensin II receptor blocker	33 (36)	59 (39)	92 (38)
Aldosterone antagonist	11 (12)	11 (7)	22 (9)
Renin inhibitor	1 (1)	1 (1)	2 (1)
Dual RAASi blockade[a]	19 (21)	22 (15)	41 (17)
On maximal dose[b]	42 (46)	64 (42)	106 (44)
Not on maximal dose[b]	50 (54)	87 (58)	137 (56)
Non-RAASi, non-diuretic antihypertensives	**63 (68)**	**123 (81)**	**186 (77)**
Alpha blocker	10 (11)	12 (8)	22 (9)
Beta blocker	46 (50)	82 (54)	128 (53)
Calcium channel blocker	37 (40)	75 (50)	112 (46)
Alpha-2 agonist	6 (7)	11 (7)	17 (7)
Vasodilator	2 (2)	2 (1)	4 (2)
Non-RAASi diuretics	**50 (54)**	**82 (54)**	**132 (54)**
Thiazide or thiazide-like diuretic	25 (27)	45 (30)	70 (29)
High-ceiling diuretic	29 (32)	48 (32)	77 (32)
Magnesium[c]	**8 (9)**	**16 (11)**	**24 (10)**
Insulin	**20 (22)**	**35 (23)**	**55 (23)**
Long-acting	8 (9)	14 (9)	22 (9)
Intermediate-acting	3 (3)	10 (7)	13 (5)
Short-acting	12 (13)	23 (15)	35 (14)
Combination	4 (4)	5 (3)	9 (4)
Non-insulin antidiabetic medication	**34 (37)**	**52 (34)**	**86 (35)**
Biguanides	14 (15)	20 (13)	34 (14)
Sulphonyureas	22 (24)	42 (28)	64 (26)
Other non-insulin	6 (7)	3 (2)	9 (4)

High-ceiling diurectis: loop diuretics

a. Dual RAASi blockade is defined by any combination of at least two of the following: 1) angiotensin-converting enzyme inhibitor, 2) angiotensin II receptor blocker, 3) aldosterone antagonist and 4) renin inhibitor.
b. Investigators indicated with a yes/no checkbox on the Medication Modification eCRF at the Part A Baseline visit whether the subject is on maximal RAASi dose.
c. Subjects whose medication was coded with an Anatomical Therapeutic Chemical, 4th level term of 'magnesium or magnesium compound' are counted in this row.

(Applicant's table from CSR 301 table 23, page 141)

Demographics in Part B of Study RLY5016-301: A total of 110 subjects completed Part A and were eligible for Part B. Three of these 110 subjects elected not to participate in Part B. All of the remaining 107 subjects were randomized into Part B: 52 were randomized to receive placebo and 55 were randomized to continue to receive RLY5016. Of the 107 subjects who participated in Part B of the study, 54% were male and all were white; the median age was 65 years (range: 32 to 80 years). Demographics were similar in the placebo and RLY5016 groups. Overall, 63% of subjects had type 2 DM, 46% had HF, and 97% had hypertension. These data are summarized in the tables below. In general, the two groups appeared to be well-matched.

Table 9: Demographics (Part B ITT Population)

Demographic Characteristic	Placebo N = 52	RLY5016 FOS N = 55	Total N = 107
Sex, n (%)			
Male	30 (58)	28 (51)	58 (54)
Female	22 (42)	27 (49)	49 (46)
Age at informed consent (years)			
n	52	55	107
Mean (SD)	65.0 (9.1)	65.5 (9.4)	65.3 (9.2)
Range (min, max)	32, 79	41, 80	32, 80
Quartiles (25th, median, 75th)	60, 66, 72	60, 65, 73	60, 65, 72
Age category, n (%)			
< 65 years of age	21 (40)	26 (47)	47 (44)
≥ 65 years of age	31 (60)	29 (53)	60 (56)
≥ 75 years of age	7 (13)	11 (20)	18 (17)
Race, n (%)			
White	52 (100)	55 (100)	107 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	50 (96)	54 (98)	104 (97)
Hispanic or Latino	2 (4)	1 (2)	3 (3)

(Applicant's table from CSR 301 table 26, page 146)

Table 10: Medical History Recorded at Part A Baseline (Part B ITT Population)

Medical condition		Placebo N=52	RLY5016 N=55	Total N=107
Chronic Kidney Disease	Stage 2	4 (8%)	8 (15%)	12 (11%)
	Stage 3a	11 (21%)	11(20%)	22 (21%)
	Stage 3b	14 (27%)	15 (27%)	29 (27%)
	Stage 4 or worse	23 (44%)	21 (38%)	44 (41%)
Type II diabetes		33 (63%)	34 (62%)	67(63%)
Heart Failure		22 (42%)	27 (49%)	49 (46%)
Prior myocardial infarction		14 (27%)	18 (33%)	32 (30%)
Hypertension		50 (96%)	54 (98%)	104 (97%)

(Reviewer's table)

Baseline medications of interest in Part B are summarized in the table below. With regard to RAASi use, 70% of Part B subjects were on ACEIs, 37% were on ARBs and 7% were on AAs. The proportion of subjects using a particular RAASi class was generally similar in the placebo and RLY5016 groups although ARB use was somewhat greater in the RLY5016 group than in the placebo group (44% and 31%, respectively). Overall, at the Part B baseline, 15% (16/107) of Part B subjects were receiving dual RAASi blockade which was similar to the percentage of subjects receiving dual blockade at baseline in Part A (17%). Based on the investigator's assessment, 39% (42/107) of the Part B subjects were on a maximal RAASi medication dose including 40% in the placebo group and 38% in the RLY5016 group.

Table 11: Part B Baseline Concomitant Medication Use (Part B ITT Population)

Medication Class	Placebo N = 52 n (%)	RLY5016 FOS N = 55 n (%)	Total N = 107 n (%)
RAASi	**52 (100)**	**55 (100)**	**107 (100)**
Angiotensin-converting-enzyme inhibitor	38 (73)	37 (67)	75 (70)
Angiotensin II receptor blocker	16 (31)	24 (44)	40 (37)
Aldosterone antagonist	4 (8)	4 (7)	8 (7)
Renin inhibitor	0	0	0
Dual RAASi blockade[a]	6 (12)	10 (18)	16 (15)
On maximal dose[b]	21 (40)	21 (38)	42 (39)
Not on maximal dose[b]	31 (60)	34 (62)	65 (61)
Non-RAASi, non-diuretic antihypertensives	**43 (83)**	**44 (80)**	**87 (81)**
Alpha blocker	4 (8)	5 (9)	9 (8)
Beta blocker	32 (62)	33 (60)	65 (61)
Calcium channel blocker	22 (42)	23 (42)	45 (42)
Alpha-2 agonist	3 (6)	4 (7)	7 (7)
Vasodilator	0	0	0
Non-RAASi diuretics	**27 (52)**	**28 (51)**	**55 (51)**
Thiazide or thiazide-like diuretic	11 (21)	16 (29)	27 (25)
High-ceiling diuretic	20 (38)	16 (29)	36 (34)
Magnesium[c]	**6 (12)**	**9 (16)**	**15 (14)**
Insulin	**15 (29)**	**13 (24)**	**28 (26)**
Long-acting	5 (10)	6 (11)	11 (10)
Intermediate-acting	6 (12)	4 (7)	10 (9)
Short-acting	11 (21)	8 (15)	19 (18)
Combination	1 (2)	2 (4)	3 (3)
Non-insulin antidiabetic medication	**20 (38)**	**22 (40)**	**42 (39)**
Biguanides	5 (10)	9 (16)	14 (13)
Sulphonyureas	17 (33)	18 (33)	35 (33)
Other non-insulin	1 (2)	2 (4)	3 (3)

a. Dual RAASi blockade is defined by any combination of at least two of the following: 1) angiotensin-converting enzyme inhibitor, 2) angiotensin II receptor blocker, 3) aldosterone antagonist, and 4) renin inhibitor.
b. Investigators indicated with a yes/no checkbox on the Medication Modification eCRF at the Part A Baseline visit whether the subject is on maximal RAASi dose.
c. Subjects whose medication was coded with an Anatomical Therapeutic Chemical, 4th level term of 'magnesium' or magnesium compound' are counted in this row.

(Applicant's table from CSR301 table 28,page 150)

Reviewer's comment: In general, baseline demographics were similar between the treatment and placebo arms in Part B. The study population appears to be representative of the population at risk for hyperkalemia.

6.1.3 Subject Disposition

The following discussion focuses on subject disposition in Parts A and B of the pivotal study.

Part A Disposition: In the pivotal study, a total of 395 subjects were screened of which 243 subjects (62%) were enrolled in Part A including 92 in Dose Group 1 and 151 in Dose Group 2. All 243 subjects who were enrolled in Part A received at least one dose of RLY5016. Of the 243 subjects enrolled in Part A, 64% were enrolled at sites in 3 countries in Eastern Europe that were not EU member states (Georgia [12 sites], Ukraine [9 sites] and Serbia [3 sites]; subsequently referred to as non-EU); 27% were enrolled at sites in 6 countries in the EU (Hungary [8 sites], Croatia [5 sites], Denmark [4 sites], Slovenia [2 sites], Italy [1 site] and the Czech Republic [1

site]); and 9% were enrolled at 14 sites in the US. The number of subjects enrolled at each site ranged from 1 to 13.

Subject disposition in Part A is summarized in the table below. Of the 243 subjects who were enrolled, 219 (90.1%) subjects completed the 4-week study in Part A. Reasons for early withdrawal from Part A included: adverse events (10), high serum potassium (3), low serum potassium (1), eGFR < 10 mL/min/1.73 m^2 or need for dialysis (2), subject's decision to withdraw from the study (5), noncompliance with study drug (1), and protocol violation (2). Subjects who were enrolled in Part A but did not continue into Part B (i.e., withdrew early from Part A or completed Part A but were not randomized into Part B) were to complete a 1- to 2-week follow-up period to Part A. A total of 136 subjects did not participate in Part B and 121 (89%) of these subjects completed the Part A follow-up.

Table 12: Disposition in Part A (ITT Population)

	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 (%)
Part A Treatment Phase[a]	**92 (100)**	**151 (100)**	**243 (100)**
Completed Part A	85 (92)	134 (89)	219 (90)
Eligible for Part B	16 (17)	94 (62)	110 (45)
Not eligible for Part B[b]	69 (75)	40 (26)	109 (45)
Central laboratory serum K^+ not ≥ 5.5 mEq/L at ABL	64 (70)	33 (22)	97 (40)
AW4/BBL local laboratory serum K^+ not in normal range of 3.8 to < 5.1 mEq/L	11 (12)	11 (7)	22 (9)
Not taking RAASi	2 (2)	0	2 (1)
Not on 8.4 to 50.4 g/day dose of RLY5016 FOS	5 (5)	2 (1)	7 (3)
Did not complete Part A	7 (8)	17 (11)	24 (10)
Adverse event	2 (2)	8 (5)	10 (4)
Withdrawal by subject	2 (2)	3 (2)	5 (2)
Met protocol-specified withdrawal criteria (high serum potassium results)	1 (1)	2 (1)	3 (1)
Met protocol-specified withdrawal criteria (eGFR decrease to < 10 mL/min/1.73m^2 or need for dialysis)	2 (2)	0	2 (1)
Protocol violation	0	2 (1)	2 (1)
Met protocol-specified withdrawal criteria (low serum potassium results)	0	1 (1)	1 (<1)
Non-compliance with study drug	0	1 (1)	1 (<1)
After Part A Treatment Phase			
Follow-up visits in Part A	77 (84)	58 (38)	135 (56)
Completed follow-up in Part A	72 (78)	49 (32)	121 (50)
Did not complete follow-up in Part A	5 (5)	9 (6)	14 (6)
Randomized into Part B	15 (16)	93 (62)	108 (44)
Eligible, received IP and included in the ITT population	15 (16)	92 (61)	107 (44)
Not eligible, did not receive IP and not included in the ITT population[c]	0	1 (1)	1 (<1)

ABL = Part A Baseline; AW4 = Part A Week 4; BBL = Part B Baseline; IP = investigational product
a. The End of Part A Treatment eCRF indicated whether the subject completed the Part A Treatment Phase.
b. Subjects is not met the criterion for Part B via a checkbox on the Inclusion/ Exclusion Criteria eCRF.
c. One Dose Group 2 subject (140109) was not eligible for Part B, but was randomized in error. This error was identified before the subject received any randomized IP and the subject subsequently entered into Part A follow-up. Because this subject was not eligible for Part B, did not receive any randomized IP and had no Part B assessment beyond Part A Week 4/Part B Baseline, this subject was not included in the ITT population of Part B.
(Applicant's table from CSR 301 table 14, page 116)

Part B Disposition: Of the 243 subjects enrolled in Part A, 110 subjects were eligible for Part B. Of these, three (3) subjects who completed Part A and were eligible for Part B elected not to continue into Part B. One hundred and seven (107) subjects were randomized into Part B. One subject, whose Part A baseline serum potassium was < 5.5 mEq/L and who was, therefore, ineligible for Part B, was inadvertently randomized into Part B (placebo group) as a result of a clerical error that was detected before the subject had received any randomized investigational product in Part B (and prior to the collection of any Part B data from the subject).

Of the 107 subjects who participated in Part B of the study, 79% were enrolled at sites in 3 countries in Eastern Europe that were not EU member states (Georgia [11 sites], Ukraine [6 sites] and Serbia [3 sites]), 17% were enrolled at sites in 6 countries in the EU (Hungary [5 sites], Croatia [2 sites], Slovenia [1 site], the Czech Republic [1 site], Denmark [1 site] and Italy [1 site]) and 4% were enrolled at 3 sites in the US. The proportion of subjects from sites in non-EU countries was greater in Part B than in Part A (79% and 64%, respectively). The number of subjects randomized into Part B at each site ranged from 1 to 10.

As the primary efficacy endpoint was determined during the first 4 weeks of Part B, subject disposition in Part B is summarized both through Week 4 of Part B and through the whole Part B phase (Week 8):

- Disposition through Week 4 of Part B: Of the 107 subjects who participated in Part B, 45 (89%) subjects in the placebo group and 50 subjects (91%) in the RLY5016 group were evaluated at the end of Week 4 of Part B for the primary endpoint analysis.
- Disposition through the entirety (Week 8) of Part B: Of the 107 subjects who participated in Part B, 30 (58%) subjects in the placebo group and 45 (82%) subjects in the RLY5016 group completed the Part B, 8-week study.

Of the 107 subjects who participated in Part B, 96 subjects (90%) completed the protocol-specified 1- to 2-week follow-up as shown the table below.

Table 13: Disposition in Part B (ITT Population)

	Placebo N = 52 n (%)	RLY5016 FOS N = 55 n (%)	Total N = 107 n (%)
Part B Randomized Withdrawal Phase			
Remained on IP through Part B Week 4[a]	45 (87)	50 (91)	95 (89)
Discontinued IP prior to Part B Week 4	7 (13)	5 (9)	12 (11)
Remained on IP through Part B Week 8[b]	30 (58)	45 (82)	75 (70)
Discontinued IP prior to Part B Week 8	22 (42)	10 (18)	32 (30)
After Part B Randomized Withdrawal Phase			
Completed follow-up in Part B	45 (87)	51 (93)	96 (90)
Did not complete follow-up in Part B	7 (13)	4 (7)	11 (10)

a If a subject's last dose of IP was on or after Day 26 (relative to first dose of IP in Part B), the subject is classified as remaining on IP through Part B Week 4. Otherwise, the subject is classified as discontinuing IP prior to Part B Week 4.

b If a subject's last dose of IP was on or after Day 54 (relative to first dose of IP in Part B) or if the End of Study eCRF indicated that subject's Part B treatment status was 'Completed', the subject is classified as remaining on IP through Part B Week 8. Otherwise, the subject is classified as discontinuing IP prior to Part B Week 8. Investigators recorded the treatment status as 'complete' for all subjects whose last dose of IP was on or after Day 54.

(Applicant's table from CSR301 table 17 page 124)

A larger proportion of subjects in the placebo group (42% [22/52]) than in the RLY5016 group (18% [10/55]) withdrew early from Part B, primarily because more subjects in the placebo arm met the protocol-specified withdrawal criteria for a high serum potassium result. Otherwise, the reasons for withdraw and proportion of withdrawls were similar in the two arms.

Table 14: Reasons for Not Completing Part B (Part B ITT Population)

	Placebo N = 52 n (%)	RLY5016 FOS N = 55 n (%)	Total N = 107 n (%)
Completed Part B	**30 (58)**	**45 (82)**	**75 (70)**
Did not complete Part B	**22 (42)**	**10 (18)**	**32 (30)**
Met protocol-specified withdrawal criteria (high serum potassium results)	14 (27)	2 (4)	16 (15)
Met protocol-specified withdrawal criteria (low serum potassium results)	1 (2)	2 (4)	3 (3)
Met protocol-specified withdrawal criteria (serum potassium results)	2 (4)	1 (2)	3 (3)
Adverse event	1 (2)	1 (2)	2 (2)
Met protocol-specified withdrawal criteria (eGFR decrease to < 10 mL/min/1.73m^2 or need for	1 (2)	1 (2)	2 (2)
Physician decision	1 (2)	1 (2)	2 (2)
Death	1 (2)	0	1 (1)
Lost to follow-up	0	1 (2)	1 (1)
Non-compliance with study drug	0	1 (2)	1 (1)
Withdrawal by subject	1 (2)	0	1 (1)

(Applicant's table from CSR301 table 18 page 126)
*In the third category of met protocol –specified withdraw criteria *(*Serum potassium results) means that satisfied a protocol-specified withdrawal criteria. For these 3 subjects, the serum potassium values from the local laboratory indicated that the 2 subjects in the placebo group were discontinued because of high serum potassium and the 1 subject in the RLY5016 group was discontinued because of low serum potassium.

6.1.4 Analysis of Primary Endpoint(s)

Primary endpoint in Part A: The primary efficacy endpoint for Part A was the change in serum potassium from the Part A Baseline to the Part A Week 4 visit; the mean change was estimated using a longitudinal repeated measures model. As shown in the table below, the mean change in serum potassium from the Part A Baseline to Part A Week 4 was -1.01 mEq/L [95% CI: (-1.07, -0.95); $p < 0.001$). Since the estimated maximum change in serum potassium from the Part A Baseline that could be expected due to undetected hemolysis in serum potassium samples was 0.36 mEq/L, the applicant prespecified and the Division agreed that the decrease in serum potassium from the Part A Baseline to Part A Week 4 would need to be $\geq$ 0.7 mEq/L (doubling of 0.36 mEq/L) to support efficacy. Therefore, the Part A primary efficacy endpoint was met (analysis confirmed by FDA Statistical Reviewer, Dr. Fanhui Kong).

Table 15: Estimated Change in Serum Potassium (mEq/L) (Part A ITT Population)

	Dose Group 1 5.1 to < 5.5 mEq/L N = 90		Dose Group 2 5.5 to < 6.5 mEq/L N = 147		Total 5.1 to < 6.5 mEq/L N = 237		
Visit[a]	Mean ± SE	95% CI	Mean ± SE	95% CI	Mean ± SE	95% CI	p-value[c]
Part A Day 3[b]	-0.34 ± 0.042	(-0.43, -0.26)	-0.51 ± 0.038	(-0.58, -0.43)	-0.45 ± 0.030	(-0.51, -0.39)	
Part A Week 1	-0.47 ± 0.047	(-0.56, -0.37)	-0.87 ± 0.042	(-0.95, -0.78)	-0.71 ± 0.032	(-0.78, -0.65)	
Part A Week 2	-0.63 ± 0.051	(-0.73, -0.53)	-1.09 ± 0.039	(-1.17, -1.01)	-0.91 ± 0.031	(-0.97, -0.85)	
Part A Week 3	-0.68 ± 0.057	(-0.79, -0.57)	-1.23 ± 0.039	(-1.30, -1.15)	-1.02 ± 0.032	(-1.08, -0.95)	
Part A Week 4	-0.65 ± 0.049	(-0.74, -0.55)	-1.23 ± 0.040	(-1.31, -1.16)	-1.01 ± 0.031	(-1.07, -0.95)	< 0.001

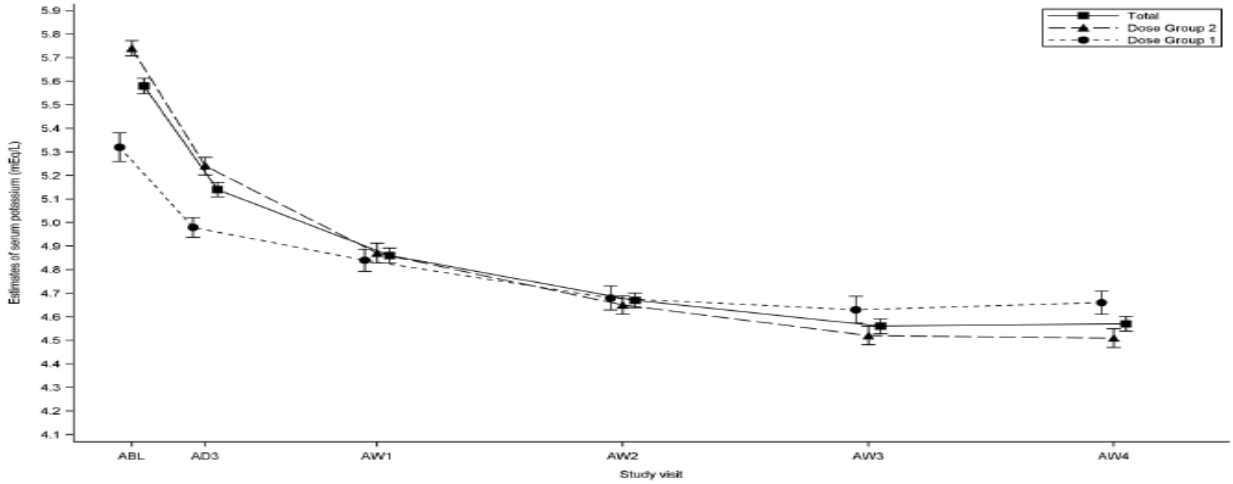
a. Visits are determined by windows defined in terms of days relative to first dose of RLY5016 FOS during Part A.
b. The estimates for Part A Day 3 come separately from an ANCOVA model with Part A Day 3 measurement as the response variable and the same covariates listed for the longitudinal model. Estimates for the starting dose groups come from running the ANCOVA model separately on the cohort of subjects in each dosing group. This analysis includes the total ITT population of Part A with a baseline and a Part A Day 3 result.
c. The p-value comes from a test comparing the mean change in serum potassium at Part A Week 4 to zero.

(Applicant's table from CSR301 table 35, page 161).

Of note, 6 of the 243 subjects in the Part A ITT Analysis Population did not have at least one post-baseline serum potassium at Week 1 or at any of the subsequent weekly follow-up visits because of early withdrawal from Part A; these 6 subjects were not included in the Part A primary efficacy endpoint analysis.

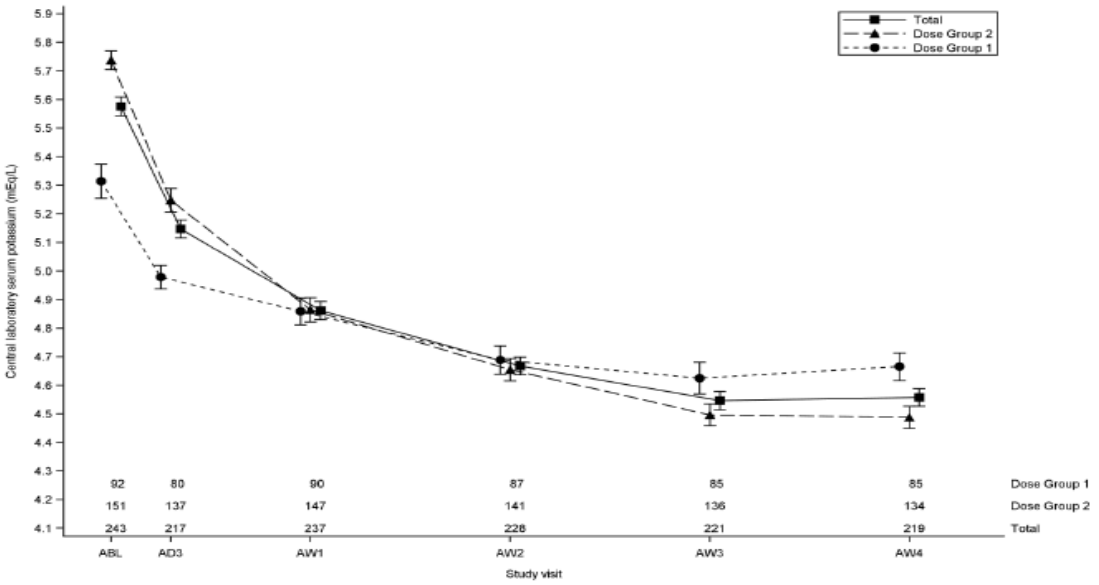
The model-based estimates of the mean serum potassium levels over time (Baseline, Day 3, Week 1, Week 2, Week 3, Week 4) and the observed mean serum potassium over time in Part A are displayed in the figures below. The observed means were very similar to the corresponding model-based estimates of the means.

Figure 4: Modelled Means with SE of Serum Potassium (mEq/L) over Time (Part A ITT Population)



(Applicant's figure 6 from CSR 301, page 166)

Figure 5: Observed Means with SE of Serum Potassium (mEq/L) over Time (Part A ITT Population)



(Applicant's figure 7 from CSR 301, page 168)

Primary endpoint in Part B: The primary efficacy endpoint for Part B was the change from the Part B Baseline serum potassium to either the Part B Week 4 visit, if the subject's serum potassium remained ≥ 3.8 mEq/L and < 5.5 mEq/L up to the Part B Week 4 visit, or the earliest Part B visit at which the subject's serum potassium was < 3.8 mEq/L or ≥ 5.5 mEq/L. The estimated difference in the median change from the Part B baseline (placebo minus RLY5016) was 0.72 mEq/L (95% CI of 0.46 to 0.99; p<0.001 for between-group difference in mean ranks of change). Therefore, the Part B primary efficacy endpoint was also met (analysis confirmed by FDA Statistical Reviewer, Dr. Fanhui Kong).

Table 16: Change in Serum Potassium from Part B Baseline to Part B Week 4 or the First Local Laboratory Serum Potassium Result of < 3.8 mEq/L or ≥ 5.5 mEq/L (Part B ITT Population)

Estimated Median Change in Serum K^+ (mEq/L) (quartiles)		Difference in Median Change (mEq/L)	
Placebo N = 52	RLY5016 FOS N = 55	Estimate (95% CI)	p-value
0.72 (0.22, 1.22)	0.00 (-0.30, 0.30)	0.72 (0.46, 0.99)	< 0.001

(Applicant's table 41 from CSR 301, page 180)

As shown in the table below, the Part B Baseline serum potassium levels were similar in the placebo and RLY5016 groups. The difference between groups at Week 4 was maintained at Week 8.

Table 17: Serum Potassium Level (mEq/L) in the Placebo and RLY5016 Arms at Baseline, Week 4, and Week 8 in Part B

Visit		Placebo	RLY5016	Change from baseline	
				Placebo	*RLY5016*
Baseline	n	52	54	-	-
	Mean (SD)	4.45 (0.34)	4.49 (0.43)	-	-
Week 4	n	45	50	45	49
	Mean (SD)	4.95 (0.48)	4.55 (0.39)	0.50 (0.50)	0.02 (0.55)
Week 8	n	29	45	29	44
	Mean (SD)	4.85 (0.45)	4.52 (0.40)	0.45 (0.45)	0.00 (0.56)

(Reviewer's table based on CSR 301 table 14.4.6.2.2, page 381-384)

Reviewer comments: The primary efficacy endpoint was reached in both Part A and Part B. Each part can be considered a separate "pivotal" study, supporting efficacy. According to the applicant, sensitivity analyses (data not shown here) addressing missing data and protocol deviations in a few subjects produced results that were similar to the results described above. According to Dr. Fanhui Kong's review, these analyses have been confirmed.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints in Part A: The main secondary endpoint for Part A was the proportion of subjects with a potassium level in the target range of 3.8 to < 5.1 mEq/L after 4 weeks of treatment in Part A. Overall, the estimated proportion of subjects with a serum potassium level in the Part A target range at Week 4 was 76% [95% CI: (70%, 81%)], with similar percentages in each starting dose group as shown in the table below. Three percent of subjects (8/243) had a serum potassium value below the target range and 11% (27/243) had a value above the target range at Week 4.

Table 18: Estimated Percentage of Subjects Having Serum Potassium Values within the Target Range of 3.8 to < 5.1 mEq/L at Part A Week 4 (Part A ITT Population)

Percentage n (%)	Dose Group 1 5.1-5.5 mEq/L N=92 (%)	Dose Group 2 5.5-6.5 mEq/L N=151(%)	Total 5.1-6.5 mEq/L N=243(%)
Part A Week 4 Serum K^+ 3.8 to 5.1 mEq/L	68 (74)	116 (77)	184 (76)
Did not complete Part A	24 (26)	35 (23)	59 (24)
Part A Week 4 Serum $K^+ < 3.8$ mEq/L	1 (1)	7 (5)	8 (3)
Part A Week 4 Serum $K^+ \geq 5.1$ mEq/L	16 (17)	11 (7)	27 (11)

(Reviewer's table based on CSR 301 table 36, page 164)

Secondary endpoints in Part B: The main secondary endpoints for Part B were (1) the proportion of subjects with a serum potassium ≥ 5.5 mEq/L at any time after the Part B Baseline through the

Part B Week 8 visit and (2) the proportion of subjects with a serum potassium 5.1 mEq/L at any time after the Part B Baseline through the Part B Week 8 visit.

The estimated proportion of subjects with a serum potassium ≥ 5.5 mEq/L was 60% in the placebo group and 15% in the RLY5016 group; the estimated difference in percentages (placebo minus RLY5016) was 45% ($p < 0.001$). The estimated proportion of subjects with a serum potassium ≥ 5.1 mEq/L was 91% in the placebo group and 43% in the RLY5016; the estimated difference in percentages (placebo minus RLY5016) was 48% ($p < 0.001$).

Table 19: Secondary Efficacy Outcome Results (Part B ITT Population)

	Stratified Percentages (95% CI)			
Secondary Outcome	Placebo N = 52	RLY5016 FOS N = 55	Difference[a]	p-value
Having a serum $K^+ \geq 5.5$	60 (47, 74)	15 (6, 24)	45 (29, 61)	< 0.001
Having a serum $K^+ \geq 5.1$	91 (83, 99)	43 (30, 56)	48 (33, 63)	< 0.001

a. Difference is calculated as placebo - RLY5016

(Applicant's table from CSR 301 table 41, page 183)

6.1.6 Other Endpoints:

The applicant conducted various exploratory analyses; some of these are described below.

Study RLY5016-301: Part A

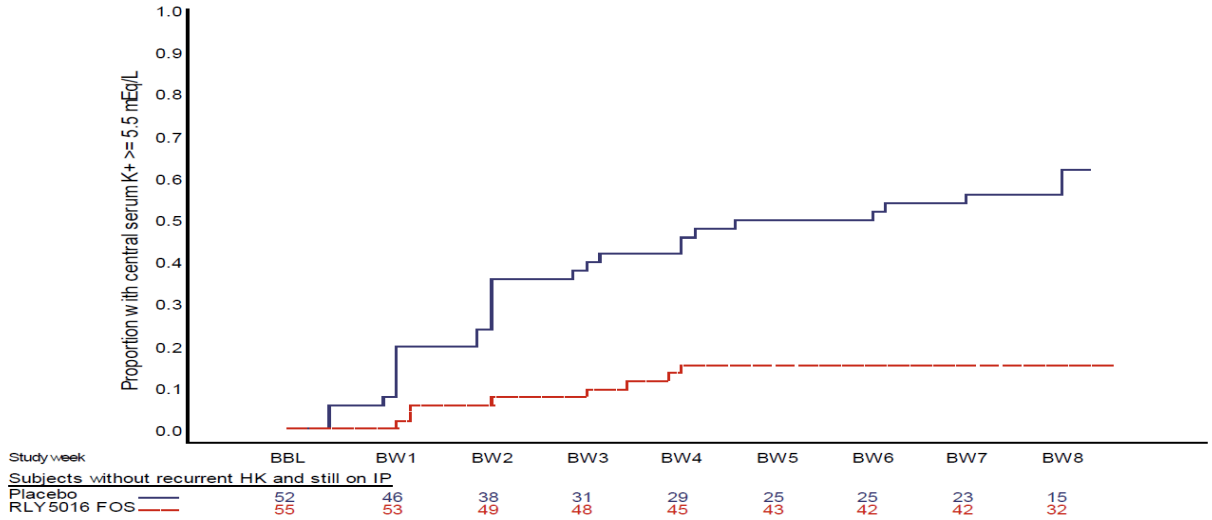
Maximum Reduction in Serum Potassium during Part A: The maximum reduction from baseline in serum potassium during Part A was determined for all subjects who had a central laboratory serum potassium value at baseline and at least one post-baseline visit (n=234). The maximum reduction was > 0.5 mEq/L for 88% (205/234), 0.3 to 0.5 mEq/L for 8% (19/234) and < 0.3 mEq/L (but > 0.0 mEq/L) for 3% (6/234).

Four subjects, three in Dose Group 1 and one in Dose Group 2, had no reduction from baseline in serum potassium (central laboratory) at any time during Part A. For two of these four subjects the baseline serum potassium was <5.1 mEq/L. One subject withdrew early on Day 3 because of moderate vomiting that started on Day 1 and resolved after withdrawal from study; the subject's central serum potassium level was 5.4 mEq/L at baseline and 5.9 mEq/L on Day 3.

Study RLY5016-301: Part B

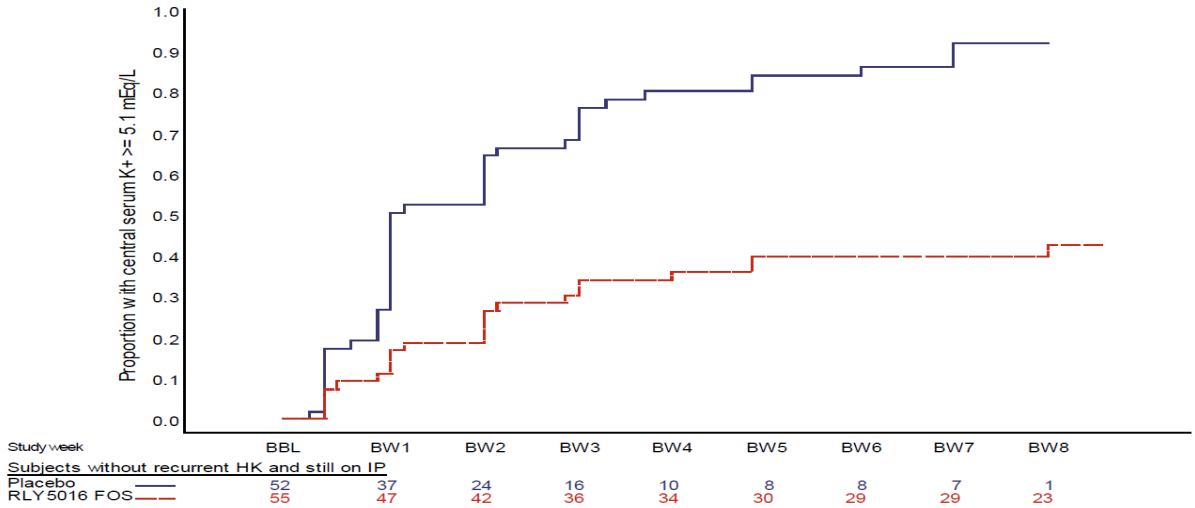
Time to First Occurrence of a Central Laboratory Serum Potassium: (1) ≥ 5.5 mEq/L and (2) ≥ 5.1 mEq/L: The time to the first occurrence of a central laboratory serum potassium (1) ≥ 5.5 mEq/L and (2) ≥ 5.1 mEq/L during Part B were analyzed as exploratory outcomes. As shown in the figures below, for both of these outcomes, the estimated proportion in the placebo group was higher than that in the RLY5016 group starting at the first follow-up visit (Day 3); the difference between the treatment group proportions increased over time in Part B.

Figure 6: Time to First Serum K+ ≥ 5.5 mEq/L (Part B ITT Population)



Abbreviations: BBL = Part B Baseline; BW1 = Part B Week 1; BW2 = Part B Week 2; BW3 = Part B Week 3; BW4 = Part B Week 4; BW5 = Part B Week 5; BW6 = Part B Week 6; BW7 = Part B Week 7; BW8 = Part B Week 8;
(Applicant's figure from CSR 301 figure 10, page 196)

Figure 7: Time to First Serum K+ ≥ 5.1 mEq/L (Part B ITT Population)



Abbreviations: BBL = Part B Baseline; BW1 = Part B Week 1; BW2 = Part B Week 2; BW3 = Part B Week 3; BW4 = Part B Week 4; BW5 = Part B Week 5; BW6 = Part B Week 6; BW7 = Part B Week 7; BW8 = Part B Week 8;
(Applicant's figure from CSR 301 figure 11, page 197)

Management of Hyperkalemia in Part B: Exploratory analyses assessed the pattern of change in both serum potassium and RAASi dose (reduction or discontinuation) through Part B Week 8. The table below is a summary of the proportions of subjects in the placebo and RLY5016 group who required protocol-specified interventions for management of recurrent hyperkalemia during Part B. Overall, 73% of RLY5016 for Oral Suspension subjects compared to 33% of placebo subjects did not require a protocol-specified intervention for recurrent hyperkalemia during Part B and completed Part B.

Table 20: Management of Recurrent Hyperkalemia during Part B (Part B ITT Population)

Placebo N=52		RLY5016 FOS N=55	
Outcome	**n (%)**	**Outcome**	**n (%)**
Management for recurrent hyperkalemia		**Management for recurrent hyperkalemia**	
RAASi dose reduction by 50%[a]	5 (10)	RLY5016 FOS dose increase[c]	6 (11)
RAASi discontinuation[b]	27 (52)	RAASi discontinuation[b]	3 (5)
Neither and completed Part B	17 (33)	Neither and completed Part B	40 (73)
Neither and discontinued prior to Week 8	3 (6)	Neither and discontinued prior to Week 8	6 (11)

a. Subjects who reduced their RAASi dose by 50% or to the next dose available below 50% without discontinuing their RAASi completely
b. Subjects who discontinued all RAASi medication for any reason
c. Subjects who increased their RLY5016 FOS dose without discontinuing their RAASi completely

Proportion of Subjects at Part B Week 8: (1) Taking any RAASi Dose (2) Taking a Maximum RAASi Dose: At the end of Week 8, a greater proportion of subjects in the RLY5016 group as compared to the placebo group was taking any RAASi dose (78% vs 37%) and a maximum RAASi dose, as assessed by the investigator (25% vs 12%).

6.1.7 Subpopulations

The results of subgroup analyses for the primary endpoints in Parts A and B are discussed below.

For Part A, subgroup analyses for both primary and secondary endpoints were performed by age (<65 years, ≥ 65 years), gender, primary diseases (type 2 DM and heart failure), Part A Baseline (central-laboratory) serum potassium (< 5.5 mEq/L, ≥ 5.5 mEq/L), investigator's assessment of whether the subject was on a maximal RAASi medication dose at baseline and region (non-EU countries, EU countries combined with US). As 98% of the subjects were white, no subgroup analysis was performed by race in Part A.

Part A primary endpoint by baseline potassium level: The magnitude of the mean change in serum potassium (primary endpoint) was greater in the subgroup with a baseline serum potassium ≥ 5.5 mEq/L as compared to the subgroup with a baseline serum potassium < 5.5 mEq/L.

Part A primary endpoint by gender**:** There was a slightly greater mean change in serum potassium in females than in males (-1.12 mEq/L in females vs -0.93 mEq/L in males).

Part A primary and secondary endpoints by region (non-EU, EU combined with US [EU+US])**:** In the analysis of the Part A primary endpoint, the mean change in serum potassium was -1.15 mEq/L for sites in non-EU countries and -0.75 mEq/L for the EU+US. Of note, the mean serum potassium at the Part A baseline was 0.3 mEq/L higher in non-EU countries (5.7 mEq/L) as compared to the EU+US (5.4 mEq/L). Consistent with the findings for the Part A primary endpoint, in the analysis of the Part A secondary endpoint, the estimated percentage of subjects within the Part A target range was greater (81%) for non-EU countries than for EU+US (66%).

As shown in the table below, there were no differences among the other subgroup that were analyzed in Part A.

Table 21: Part A Primary Efficacy Outcome by Subgroups: Estimated Change in Serum Potassium (mEq/L) from Part A Baseline to Part A Week 4 (Part A ITT Population)

	Dose Group 1 5.1 to < 5.5 mEq/L N = 90			Dose Group 2 5.5 to < 6.5 mEq/L N = 147			Total 5.1 to < 6.5 mEq/L N = 237				
Subgroup	**n**	**Mean ± SE**	**95% CI**	**n**	**Mean ± SE**	**95% CI**	**n**	**Mean ± SE**	**95% CI**	**p-value[a]**	**Interaction p-value[b]**
Part A ITT population	**90**	**-0.65 ± 0.049**	**(-0.74, -0.55)**	**147**	**-1.23 ± 0.040**	**(-1.31, -1.16)**	**237**	**-1.01 ± 0.031**	**(-1.07, -0.95)**	**< 0.001**	
Type 2 diabetes mellitus[c]											0.77
Present	52	-0.65 ± 0.066	(-0.78, -0.52)	86	-1.22 ± 0.051	(-1.32, -1.12)	138	-1.00 ± 0.040	(-1.08, -0.92)	< 0.001	
Not present	38	-0.62 ± 0.078	(-0.78, -0.47)	61	-1.26 ± 0.063	(-1.39, -1.13)	99	-1.02 ± 0.051	(-1.12, -0.92)	< 0.001	
Heart failure[d]											0.22
Present	38	-0.74 ± 0.083	(-0.91, -0.57)	62	-1.26 ± 0.068	(-1.40, -1.12)	100	-1.06 ± 0.052	(-1.16, -0.95)	< 0.001	
Not present	52	-0.57 ± 0.055	(-0.67, -0.46)	85	-1.24 ± 0.049	(-1.34, -1.14)	137	-0.98 ± 0.039	(-1.06, -0.90)	< 0.001	
ABL central laboratory serum K^+											< 0.001
<5.5 mEq/L	66	-0.48 ± 0.055	(-0.59, -0.37)	33	-0.70 ± 0.104	(-0.91, -0.49)	99	-0.54 ± 0.049	(-0.64, -0.44)	< 0.001	
≥5.5 mEq/L	24	-1.19 ± 0.107	(-1.41, -0.97)	114	-1.40 ± 0.041	(-1.48, -1.32)	138	-1.35 ± 0.041	(-1.43, -1.27)	< 0.001	
RAASi[e]											0.20
On maximal dose	41	-0.66 ± 0.068	(-0.80, -0.52)	61	-1.18 ± 0.059	(-1.29, -1.06)	102	-0.96 ± 0.045	(-1.05, -0.87)	< 0.001	
Not on maximal dose	49	-0.64 ± 0.071	(-0.79, -0.50)	86	-1.28 ± 0.053	(-1.38, -1.17)	135	-1.05 ± 0.044	(-1.13, -0.96)	< 0.001	
Sex											0.003
Male	48	-0.51 ± 0.060	(-0.63, -0.39)	88	-1.15 ± 0.054	(-1.26, -1.05)	136	-0.93 ± 0.041	(-1.01, -0.84)	< 0.001	
Female	42	-0.80 ± 0.081	(-0.96, -0.63)	59	-1.35 ± 0.058	(-1.47, -1.24)	101	-1.12 ± 0.048	(-1.21, -1.02)	< 0.001	
Age group											0.50
<65 years	39	-0.50 ± 0.079	(-0.66, -0.34)	72	-1.22 ± 0.055	(-1.33, -1.11)	111	-0.96 ± 0.045	(-1.05, -0.88)	< 0.001	
≥65 years	51	-0.73 ± 0.067	(-0.87, -0.60)	75	-1.21 ± 0.060	(-1.33, -1.09)	126	-1.01 ± 0.045	(-1.10, -0.92)	< 0.001	
Region[f]											< 0.001
Eastern Europe (non-EU)	46	-0.75 ± 0.076	(-0.91, -0.60)	107	-1.30 ± 0.044	(-1.39, -1.21)	153	-1.15 ± 0.038	(-1.23, -1.07)	< 0.001	
European Union and US	44	-0.48 ± 0.072	(-0.63, -0.33)	40	-1.07 ± 0.095	(-1.27, -0.88)	84	-0.75 ± 0.059	(-0.87, -0.64)	< 0.001	

a. The p-value comes from a test comparing the mean change in serum potassium at Part A Week 4 to zero.
b. The p-value comes from a t-test comparing the subgroups with respect to mean change in serum potassium at Part A Week 4 estimated from longitudinal model.
c. For estimates for the subgroups defined by type 2 diabetes mellitus, the longitudinal model does not include a binary covariate for type 2 diabetes mellitus.
d. For estimates for the subgroup defined by heart failure, the longitudinal model does not include a binary covariate for heart failure.
e. Investigators indicated with a yes/no checkbox on the Medication Modification eCRF at the Part A Baseline visit whether the subject is on maximal RAASi dose.
f. The countries included in Eastern Europe (non-EU) are Georgia, Ukraine and Serbia. The countries included in the European Union are Hungary, Croatia, Denmark, Italy, Slovenia and Czech Republic.

(Applicant's table from CSR 301, table 38, page 173)

Subgroup analyses for both primary and secondary endpoints in Part B include age (<65 years, ≥ 65 years), gender, primary diseases (T2DM and HF), Part A Baseline (central-laboratory) serum potassium (< 5.8 mEq/L, ≥ 5.8 mEq/L) and investigator's assessment of whether the subject was on a maximal RAASi medication dose at the Part A Baseline. Similar to Part A, 98% of the subjects were white, so no subgroup analysis was performed by race. Subgroup analyses of the Part B primary and secondary endpoints were also performed by region (non-EU countries, EU countries combined with US).

Part B primary and secondary endpoint by region (non-EU, EU combined with US [designated EU+US]): The magnitude of the increase from baseline in the placebo group was greater in the EU+US (1.39 mEq/L) than in non-EU countries (0.52 mEq/L). In both regions, the RLY5016 groups showed almost no change in serum potassium from the Part B baseline. So the difference by region in Part B resulted from a different magnitude of increase in serum potassium from baseline in the placebo groups. Examination of the baseline characteristics of Part B participants showed that the baseline eGFR in the EU/US region (mean of 27 mL/min/1.73 m^2 at the Part A baseline) was lower than the eGFR in the non-EU region (mean of 39 mL/min/1.73 m^2 at the Part A Baseline); this difference in eGFR might explain why subjects in the placebo group in the EU/US had more recurrent hyperkalemia driving a larger between-group difference for the primary endpoint in that region. However, as there were only 12 placebo subjects in the EU/US, the sample size may be too small to support analyses that could definitively conclude whether the difference by region in the magnitude of the increase in serum potassium in the placebo groups in Part B was due to eGFR, other baseline covariate or due to chance.

For the secondary endpoint, the estimated percentage of subjects with a serum potassium ≥ 5.1 mEq/L in the RLY5016 group was 90% in the EU+US and 33% in non-EU. For a serum potassium ≥ 5.5 mEq/L, the estimated percentage was 30% in the EU+US and 12% in non-EU.

Part B secondary endpoint by age (< 65 years, ≥ 65 years): The estimated percentage of subjects with a serum potassium ≥ 5.1 mEq/L was 58% for those < 65 years of age (32% difference from placebo) and 30% for those ≥ 65 years of age (63% difference from placebo). Thus, in the RLY5016 groups, the percentage of subjects with a serum potassium ≥ 5.1 mEq/L was lower in those ≥ 65 years of age than in those < 65 years of age. This was also observed in the analysis for the other Part B secondary endpoint (percentage of subjects with a serum potassium ≥ 5.5 mEq/L).

No other significant differences were observed among the other subgroups. These data are summarized in the following tables.

Table 22: Part B Primary Efficacy Outcome by Subgroups: Change in Serum Potassium from Part B Baseline to Part B Week 4 or the First Local Laboratory Serum Potassium Value of < 3.8 mEq/L or ≥ 5.5 mEq/L (Part B ITT Population)

		Difference in Median Change (mEq/L)			
Subgroup	**n (%)**	**Estimates**	**95% CI**	**p-value[a]**	**Interaction p-value[b]**
Part B ITT population	107 (100)	0.72	(0.46, 0.99)	< 0.001	---
Type 2 diabetes mellitus[c]					0.56
Present	67 (63)	0.66	(0.28, 1.03)	< 0.001	
Not present	40 (37)	0.82	(0.47, 1.17)	< 0.001	
Heart failure					0.50
Present	49 (46)	0.64	(0.29, 0.99)	< 0.001	
Not present	58 (54)	0.83	(0.42, 1.24)	< 0.001	
ABL central serum potassium[d]					0.74
<5.8 mEq/L	53 (50)	0.80	(0.44, 1.17)	< 0.001	
≥5.8 mEq/L	54 (50)	0.72	(0.34, 1.09)	< 0.001	
RAASi[e]					0.41
On maximal dose	42 (39)	0.92	(0.54, 1.29)	< 0.001	
Not on maximal dose	65 (61)	0.69	(0.32, 1.05)	< 0.001	
Sex					0.63
Male	58 (54)	0.70	(0.36, 1.04)	< 0.001	
Female	49 (46)	0.83	(0.41, 1.24)	< 0.001	
Age group					0.37
<65 years	47 (44)	0.57	(0.11, 1.03)	0.006	
≥65 years	60 (56)	0.81	(0.49, 1.14)	< 0.001	
Region[f]					0.003
Eastern Europe (non-EU)	85 (79)	0.52	(0.25, 0.78)	< 0.001	
European Union and US	22 (21)	1.39	(0.91, 1.88)	< 0.001	

ABL = Part A Baseline

a. To compare RLY5016 FOS with placebo, the differences between the mean ranks were tested using a two sided test.
b. The p-values come from two-sided t-tests comparing the differences in median change in each pair of subgroups.
c. Changes from baseline serum potassium were ranked and compared using an ANOVA model with Part A Baseline serum potassium (<5.8 or ≥ 5.8 mEq/L) included as covariate in the model.
d. Changes from baseline serum potassium were ranked and compared using an ANOVA model with type 2 diabetes mellitus (yes/no) included as covariate in the model.
e. Investigators indicated with a yes/no checkbox on the Medication Modification eCRF at the Part A Baseline visit whether the subject is on maximal RAASi dose.
f. The countries included in Eastern Europe (non-EU) are Georgia, Serbia and Ukraine. The countries included in the European Union are Croatia, Czech Republic, Denmark, Hungary, Italy and Slovenia.

(Applicant's table from CSR 301, table 43, page186)

Table 23: Estimated Median Change in Serum Potassium (mEq/L) from Part B Baseline to Part B Week 4 by Subgroup (Part B ITT Population)

		Median Change (Quartiles)	
Subgroup	**n (%)**	**Placebo**	**RLY5016 FOS**
Part B ITT Population	107 (100)	0.72 (0.22, 1.22)	0.00 (-0.30, 0.30)
Type 2 diabetes mellitus			
Present	67 (63)	0.69 (0.19, 1.29)	0.03 (-0.20, 0.30)
Not present	40 (37)	0.72 (0.32, 1.22)	-0.10 (-0.30, 0.35)
Heart failure			
Present	49 (46)	0.74 (0.44, 1.04)	0.10 (-0.30, 0.30)
Not present	58 (54)	0.78 (0.08, 1.23)	-0.05 (-0.25, 0.30)
ABL central serum potassium			
<5.8 mEq/L	53 (50)	0.80 (0.10, 1.20)	0.00 (-0.20, 0.40)
≥5.8 mEq/L	54 (50)	0.72 (0.47, 1.47)	0.00 (-0.39, 0.25)
RAASi			
On maximal dose	42 (39)	0.82 (0.62, 1.55)	-0.10 (-0.30, 0.20)
Not on maximal dose	65 (61)	0.79 (0.29, 1.39)	0.10 (-0.20, 0.30)
Sex			
Male	58 (54)	0.60 (0.13, 1.03)	-0.10 (-0.34, 0.30)
Female	49 (46)	0.93 (0.38, 1.38)	0.10 (-0.15, 0.30)
Age group			
<65 years	47 (44)	0.57 (-0.23, 0.88)	0.00 (-0.20, 0.40)
≥65 years	60 (56)	0.81 (0.51, 1.48)	0.00 (-0.35, 0.30)
Region [a]			
Eastern Europe (non-EU)	85 (79)	0.52 (0.09, 0.97)	0.00 (-0.30, 0.30)
European Union and US	22 (21)	1.32 (0.96, 1.58)	-0.08 (-0.20, 0.70)

ABL = Part A Baseline

a. The countries included in Eastern Europe (non-EU) are Georgia, Serbia and Ukraine. The countries included in the European Union are Croatia, Czech Republic, Denmark, Hungary, Italy and Slovenia.

(Applicant's table from CSR 301, table 44, page188)

Table 24: Part B Secondary Efficacy Outcome by Subgroups: Percentage of Subjects Having a Serum Potassium Value ≥ 5.1 mEq/L at Any Time through Part B Week 8 (Part B ITT Population)

	Placebo N = 52		RLY5016 FOS N = 55		Comparison of Treatment Groups		
Subgroup	Sample Size n (%)	Percentages (95% CI)	Sample Size n (%)	Percentages (95% CI)	Difference[a]	p-value[b]	Interaction p-value[c]
Part B ITT population	52 (100)	91 (83, 99)	55 (100)	43 (30, 56)	48 (33, 63)	< 0.001	---
Type 2 diabetes mellitus[d]							0.96
Present	33 (63)	89 (73, 97)	34 (62)	41 (25, 59)	48 (28, 68)	< 0.001	
Not present	19 (37)	95 (74, >99)	21 (38)	46 (25, 69)	48 (25, 72)	< 0.001	
Heart failure							0.15
Present	22 (42)	95 (77, >99)	27 (49)	36 (19, 57)	59 (41, 77)	< 0.001	
Not present	30 (58)	88 (71, 97)	28 (51)	50 (31, 69)	38 (16, 60)	0.001	
ABL central serum potassium[e]							0.20
<5.8 mEq/L	26 (50)	86 (67, 96)	27 (49)	48 (28, 68)	38 (14, 62)	0.002	
≥5.8 mEq/L	26 (50)	96 (80, >99)	28 (51)	39 (21, 59)	58 (39, 77)	< 0.001	
RAASi [f]							0.77
On maximal dose	21 (40)	95 (76, >99)	21 (38)	50 (28, 72)	45 (25, 66)	< 0.001	
Not on maximal dose	31 (60)	88 (72, 97)	34 (62)	39 (23, 57)	50 (30, 69)	< 0.001	
Sex							0.46
Male	30 (58)	91 (75, 98)	28 (51)	39 (21, 59)	54 (33, 75)	< 0.001	
Female	22 (42)	91 (71, 99)	27 (49)	47 (28, 67)	43 (21, 64)	< 0.001	
Age group							0.043
<65 years	21 (40)	90 (70, 99)	26 (47)	58 (37, 77)	33 (9, 56)	0.006	
≥65 years	31 (60)	92 (76, 99)	29 (53)	30 (15, 50)	63 (45, 81)	< 0.001	
Region[g]							< 0.001
Eastern Europe (non-EU)	40 (77)	89 (74, 96)	45 (82)	33 (19, 48)	56 (39, 73)	< 0.001	
European Union and US	12 (23)	100 (74, 100)	10 (18)	90 (55, >99)	10 (-7, 28)	0.25	

a. Difference is calculated as placebo - RLY5016 FOS.
b. The p-value comes from a Mantel-Haenszel test.
c. The interaction p-value comes from a Z-test comparing the difference in percentages between the subgroups.
d. The percentage is stratified by the Part A Baseline central serum potassium (<5.8 or ≥ 5.8 mEq/L).
e. The percentage is stratified by type 2 diabetes mellitus (yes/no).
f. Investigators indicated with a yes/no checkbox on the Medication Modification eCRF at the Part A Baseline visit whether the subject is on maximal RAASi dose.
g. The countries included in Eastern Europe (non-EU) are Georgia, Serbia, and Ukraine. The countries included in the European Union are Croatia, Czech Republic, Denmark, Hungary, Italy, and Slovenia.

(Applicant's table from CSR 301, table 46, page192)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Although the phase 3 clinical trial used a BID dosing regimen, at this time, clinical pharmacology is recommending a once daily dosing regimen to mitigate the risk of drug-drug interactions. In addition, based on their review of studies 205 and 301 and the applicant's response to the mid-cycle communication, the clinical pharmacology reviewer does not believe a higher starting dose is needed in patients with a serum potassium ≥ 5.5 mEq/L.

Justification of Starting dose: At this time, the applicant is proposing a starting dose of 8.4 grams daily in patients with a serum potassium (b) (4) In the phase 3 trial, the starting dose was 4.2 grams BID (equivalent to a daily dose of 8.4 grams) in patients with a serum potassium > 5.0

and < 5.5 mEq/L and 8.4 grams BID (equivalent to a daily dose of 16.8 grams) in patients with a serum potassium ≥ 5.5 mEq/L. Both doses showed statistically and clinically significant reductions in mean serum potassium within a short period of time with a low rate of down titration and drop out as shown the tables below. However, at this time, the clinical pharmacology review does not believe a higher starting dose is needed in patients with higher baseline serum potassium levels (see the Clinical Pharmacology Review for analyses that address this issue and final recommendations).

Table 25: Analysis of Central Laboratory Serum Potassium at Week 4 or Prior to Titration (LOCF) by RLY5016 Starting Dose (Full Analysis Set - Subjects in Study 301 Part A)

Serum Potassium (mEq/L)	**8.4 g/day N=89**	**16.8 g/day N=148**
Baseline		
Mean (SD)	5.32 (0.579)	5.74 (0.395)
Median	5.30	5.70
Quartiles (25^{th}, 75^{th})	5.10, 5.50	5.50, 5.90
Min, Max	4.3, 9.4	4.2, 7.2
Endpoint (Week 4 or prior to titration)		
Mean (SD)	4.97 (0.545)	5.01 (0.688)
Median	5.10	5.20
Quartiles (25^{th}, 75^{th})	4.60, 5.40	4.50, 5.50
Min, Max	3.3, 6.2	3.3, 6.9
LS mean (SEM)[a]	5.01 (0.071)	4.99 (0.054)
98% CI	4.87, 5.15	4.88, 5.09
Change from baseline to endpoint (Week 4 or prior to titration)		
Mean (SD)	-0.35 (0.825)	-0.73 (0.698)
Median	-0.20	-0.50
Quartiles (25^{th}, 75^{th})	-0.70, 0.10	-1.20, -0.20
Min, Max	-4.9, 1.4	-2.3, 0.6
LS mean (SEM) [a]	-0.57 (0.071)	-0.60 (0.054)
95% CI	0.71, -0.43	-0.70, -0.49
p-value for testing LS mean[b]	< 0.001	< 0.001

Endpoint value was the last assessment value on or prior to Week 4 or prior to dose titration (LOCF).

a. The baseline LS mean, SEM, and 95% CI were estimated from ANOVA models that included study and starting dose nested in study as factors; (2) Week 4 and change from baseline to Week 4 LS mean, SEM, and 95% CI were estimated from ANCOVA models that included study and starting dose nested in study as factor, and baseline value as a covariate.

b. The p-values for testing LS means equal to 0 were from the ANCOVA model described in the footnote above.

(Applicant's table from ISE table 32, page 160)

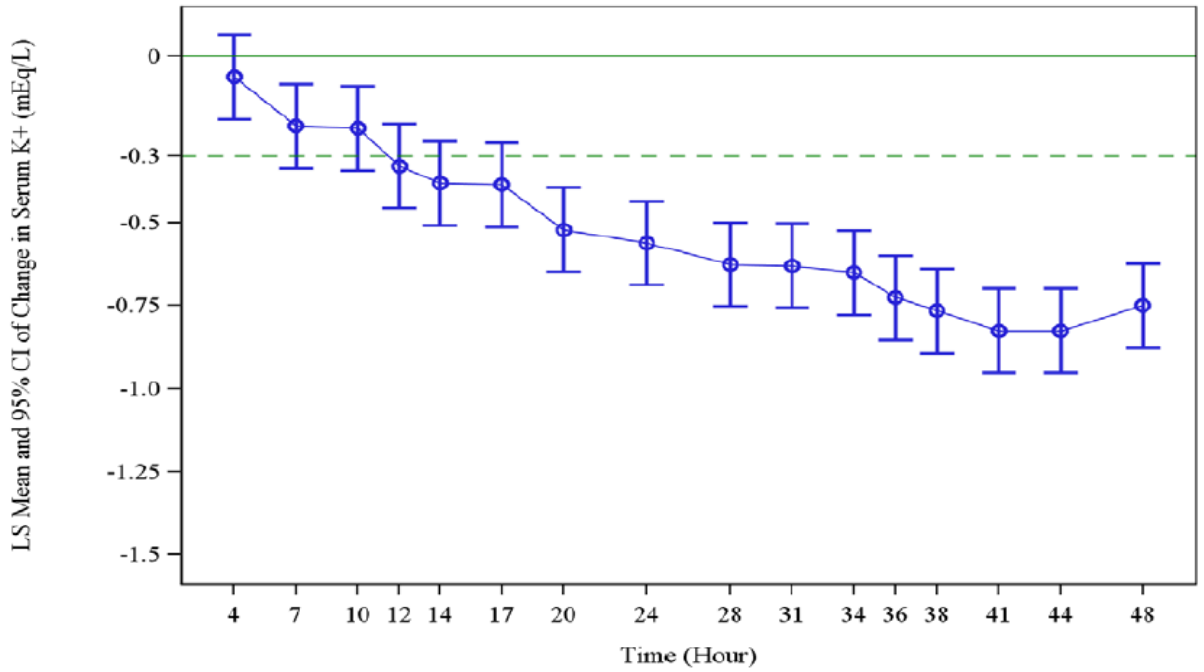
Table 26: Summary of Dose Titration during the First 4 Weeks by RLY5016 Starting Dose in ISE Local Strata 1 and 2 (Full Analysis Set)

	ISE Local Stratum 1[a]					ISE Local Stratum 2[a]				
	8.4 g/day			16.8 g/day	25.2 g/day	16.8 g/day			25.2 g/day	33.6 g/day
	Study 205 N=74	Study 301 N=89	Pooled N=163	Study 205 N=73	Study 205 N=73	Study 205 N=26	Study 301 N=148	Pooled N=175	Study 205 N=28	Study 205 N=30
Maintained starting dose (received RLY5016 FOS through Week 4 visit), n (%)	35 (47.3)	32 (36.0)	67 (41.1)	37 (50.7)	42 (57.5)	10 (38.5)	50 (33.8)	60 (34.5)	11 (39.3)	8 (26.7)
Received initial titration on or prior to Week 4, n (%)	34 (45.9)	50 (56.2)	84 (51.5)	34 (46.6)	29 (39.7)	16 (61.5)	92 (62.6)	108 (62.1)	15 (53.6)	19 (63.3)
First titrated up	32 (43.2)	50 (56.2)	82 (50.3)	21 (28.8)	16 (21.9)	12 (46.2)	86 (58.1)	98 (56.3)	10 (35.7)	12 (40.0)
First titrated down	2 (2.7)	0	2 (1.2)	13 (17.8)	13 (17.8)	4 (15.4)	6 (4.1)	10 (5.7)	5 (17.9)	7 (23.3)
Early dropout (discontinued RLY5016 FOS prior to Week 4 visit without titration), n (%)	5 (6.8)	7 (7.9)	12 (7.4)	2 (2.7)	2 (2.7)	0	6 (4.1)	6 (3.4)	2 (7.1)	3 (10.0)
Total titrations during the first 4 weeks	56	73	129	53	35	24	131	155	23	27
Up titrations	49	69	118	32	20	15	120	135	18	16
Down titrations	7	4	11	21	15	9	11	20	5	11

ISE Local Stratum 1: Study 205 subjects were required to have local laboratory baseline serum potassium > 5.0 to 5.5 mEq/L; Study 301 subjects were required to have local laboratory baseline serum potassium 5.1 to < 5.5 mEq/L.
ISE Local Stratum 2: Study 205 subjects were required to have local laboratory baseline serum potassium >5.5 to <6.0 mEq/L; Study 301 subjects were required to have local laboratory baseline serum potassium 5.5 to < 6.5 mEq/L.
a. Starting dose in g/day Rly5016.
(Applicant's table from ISE table 24, page 136)

Time to onset of action: Study 103 evaluated the time to onset of action of RLY5016. Twenty-five subjects with a serum potassium at screening of 5.5 to < 6.5 mEq/L and CKD who were not on dialysis were enrolled. Subjects received a total of 4 doses of RLY 5016 over 2 days (8.4 g BID for 2 days). The time of onset of action of RLY5016 was ~ 7 hours following the first dose. After the last dose of RLY5016 at Hour 34, mean serum potassium values continued to decline reaching a maximal reduction at Hour 41; by Hour 58 (i.e., 24 hours following the last dose), the mean serum potassium had returned to a level similar to that at the time of the last dose (i.e., Hour 34).

Figure 8: Study 103 – Least Square Means and 95% CIs of the Change from Baseline in Central Laboratory Serum Potassium Over Time (Post Baseline through Hour 48) (Full Analysis Set)



(Applicant's figure from ISE figure 7, page 47)

Dose titration: Titration of RLY5016 to maintain serum potassium within a target range was used in Studies 204, 205 and 301 Part A. Studies 204, 205, and 301 all used titration steps of 8.4 g/day RLY5016 (4.2 g BID). The interval for titration was more frequent during the early treatment period (3 days to 1 week) and in the shorter-term studies (Studies 204 and 301), and increased to longer intervals in the longer-term studies (Study 205). These data are summarized the following table.

Table 27: Dose Titration Intervals

Study Period	Minimum Titration Interval	Study
Weeks 1 to 4	Day 3 (2 days after first dose), then weekly	Studies 204, 205, and 301 Part A
Weeks 5 to 8	Weekly	Studies 204, 205, and 301 Part A
Weeks 8 to 12	Weekly	Study 205, Study 301 Part B
Weeks 12 to 52	Monthly	Study 205

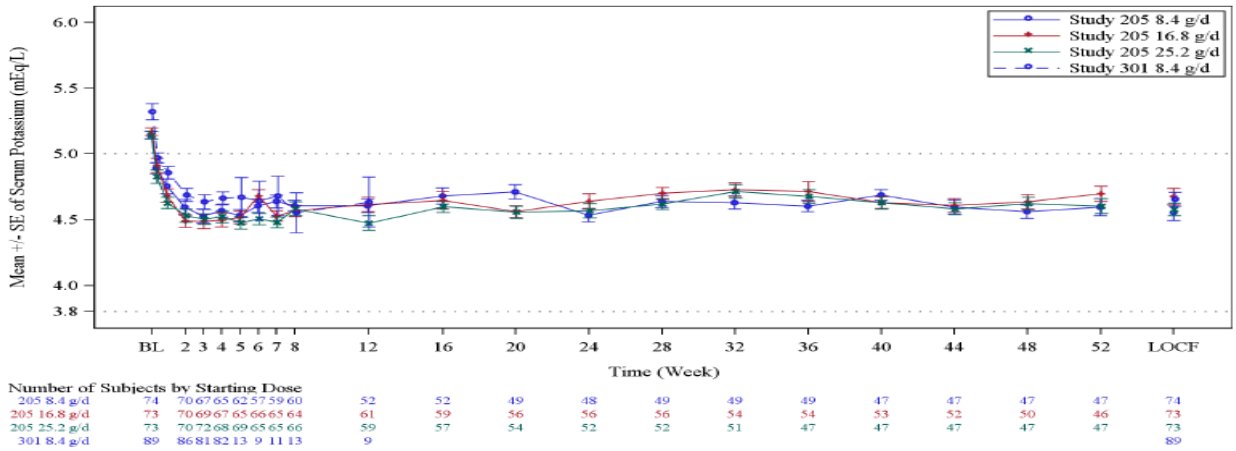
(Applicant's table from ISE table 33, page 161)

Reviewer comments: *Given the slow onset of action (about 7 hours) and long titration interval (at least two to three days), RLY5016 should not be used in the management of acute life-threatening hyperkalemia.*

6.1.9 Discussion of Persistence of Efficacy and/ Tolerance Effects

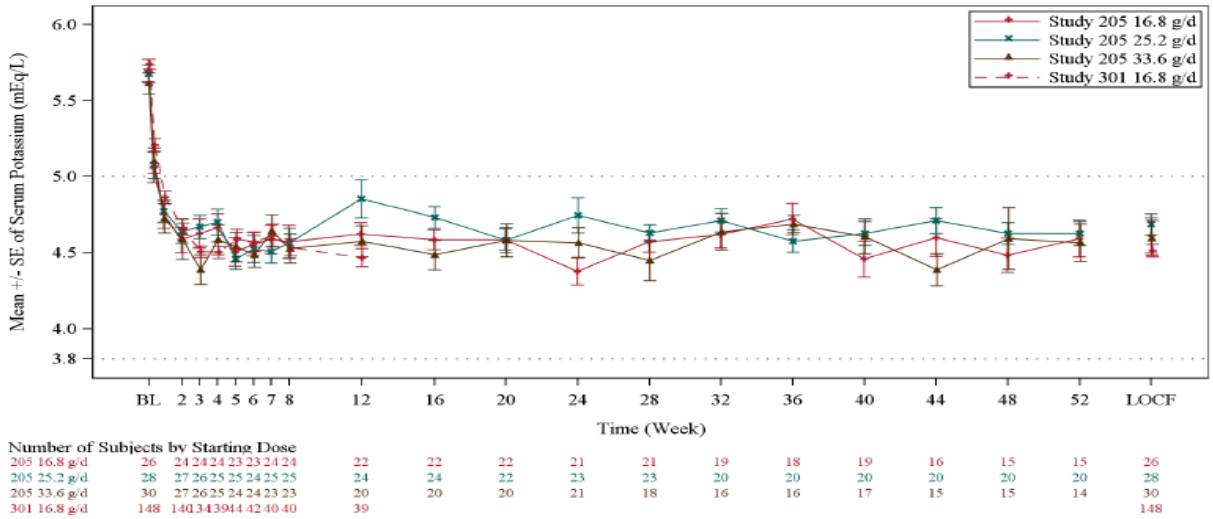
As shown in the following figures, efficacy was maintained over time with continued dosing (up to 12 weeks in Study 301 and up to 52 weeks in Study 205). Persistence of efficacy over time is further illustrated by the rise in serum potassium that occurred after withdraw of RLY5016 in Part B in Study 301.

Figure 9: Means +/- SE of Central Laboratory Serum Potassium Over Time by Starting Dose in ISE Local Stratum 1 (Full Analysis Set)



ISE Local Stratum 1: Study 205 subjects were required to have local laboratory baseline serum potassium > 5.0 to 5.5 mEq/L; Study 301 subjects were required to have local laboratory baseline serum potassium 5.1 to < 5.5 mEq/L.
For the Study 301 8.4 g/day patiromer group, time points through Week 4 include all Part A subjects, while time points after Week 4 include only subjects in Part B who received RLY5016.
(Applicant's figure from ISE figure 13, page 110)

Figure 10: Means +/- SE of Central Laboratory Serum Potassium Over Time by Starting Dose in ISE Local Stratum 2 (Full Analysis Set)



ISE Local Stratum 2: Study 205 subjects were required to have local laboratory baseline serum potassium > 5.5 to <6.0 mEq/L; Study 301 subjects were required to have local laboratory baseline serum potassium 5.5 to < 6.5 mEq/L.
Note: For the Study 301, 8.4 g/day patiromer group, time points through Week 4 include all Part A subjects, while time points after Week 4 include only subjects in Part B who received RLY5016.
(Applicant's figure 14 from ISE, page 111)

6.1.10 Additional Efficacy Issues/Analyses

Data from other studies supporting efficacy

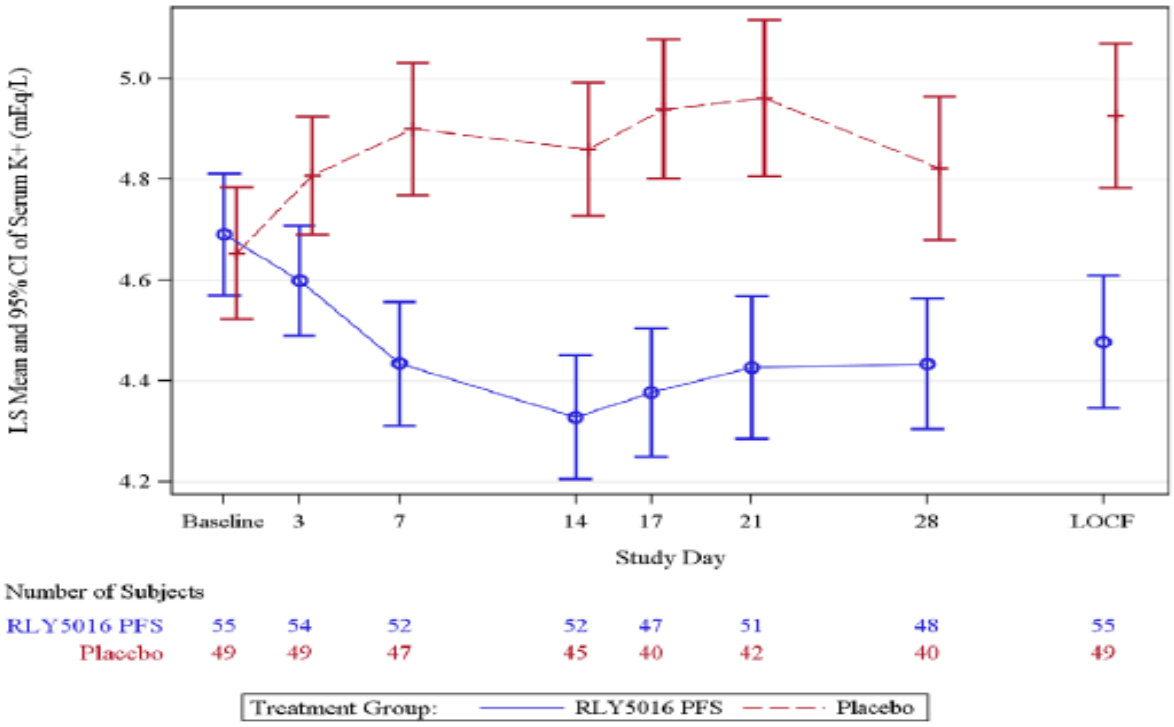
RLY 5016-205: This 1-year, phase 2, open-label, randomized, dose-ranging study was conducted to determine the optimal starting dose, efficacy, and safety of RLY5016 in treating hyperkalemia. For additional information on study design, see Section 5.3.3. The primary endpoint, the mean change from baseline in serum potassium at Week 4 (or prior to dose titration), was statistically significant for all starting dose groups within Stratum 1(serum potassium > 5.0 to 5.5 mEq/L at baseline) and Stratum 2 (serum potassium > 5.5 to < 6.0 mEq/L at baseline) The mean change at Week 4 in Stratum 1 was -0.35, -0.51, and -0.55 mEq/L for the 8.4, 16.8, and 25.2 g/day RLY 5016 starting dose groups, respectively. The mean change in Stratum 2 was -0.87, -0.97, and -0.92 mEq/L for the 16.8, 25.2, and 33.0 g/day starting dose groups, respectively.

Study RLY5016-103: This phase 1, short-term (3 days), single-arm study evaluated the time to onset of action of RLY5016. In this study, the decrease in mean serum potassium was similar to that seen in Study 205 and Part A of Study 301. For further discussion of the results of this study, see "Analysis of Clinical Information Relevant to Dosing Recommendation" in Section 6.1.8

Study RLY 5016-202: This randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of RLY5016 for prevention of hyperkalemia in subjects with heart failure with or without CKD. Eligible subjects were ≥ 18 years of age, had a history of chronic heart failure, were clinically indicated to initiate spironolactone therapy, had a serum potassium concentration of 4.3 to 5.1 mEq/L at screening and baseline, and either had: 1) CKD, with an eGFR < 60 mL/min/1.73m^2 and were receiving one or more heart failure therapies (ACEI, ARBs, or beta-blockers [BBs]); or 2) a documented history of hyperkalemia that led to discontinuation of therapy with an aldosterone antagonist, ACEI, ARB, or BB within the 6 months prior to baseline. Local laboratory values were used to determine study eligibility, discontinuation from the study, and spironolactone up titration. Subjects were randomized to 28 days of treatment with 25.2 g/day RLY5016 (administered as 12.6 g BID) (N = 56) or placebo (N = 49).

As shown in the figure below, the change from baseline in serum potassium to the end of the 28-day treatment period (LOCF) was significantly lower ($p < 0.001$) in the RLY5016 treatment group as compared with the placebo group (-0.21 vs + 0.23 mEq/L). The LS mean treatment difference (RLY5016 minus placebo) was -0.45 mEq/L (SEM: 0.09 mEq/L; 95% CI [RLY5016 minus placebo: -0.63, -0.27]). In addition, the proportion of subjects who experienced hyperkalemia (defined as a serum potassium level > 5.5 mEq/L) at any time during the 28-day treatment period was also lower in the RLY5016 than in the placebo group (7.3% versus 24.5%, respectively).

Figure 11: Study 202 - LS Mean and 95% CIs of Serum Potassium Values (mEq/L) Over Time (Full Analysis Set)



(Applicant's figure 9 from ISE, page 54)

RLY 5016-204: This open-label, single arm, dose-titration study evaluated the feasibility of individualized titration of RLY5016 according to serum potassium level for the prevention of hyperkalemia in subjects with heart failure and CKD. Sixty-three (63) subjects with eGFR < 60 mL/min/1.73m^2 and serum potassium levels of 4.3 to 5.1 mEq/L at baseline were enrolled in the study. Subjects were started on spironolactone 25 mg/day, which was up-titrated to 50 mg/day if serum potassium was < 5.1 mEq/L. Simultaneously, treatment at 16.8 g/day RLY5016 was initiated with up- or down-titration allowed in 8.4 g/day increments from 0 to 50.4 g/day of RLY5016 with the objective of keeping serum potassium in the target range of 4.0 to 5.1 mEq/L, in order to maintain serum potassium in the normal range of 3.5 to 5.5 mEq/L during the 8-week treatment period. All subjects were uptitrated to spironolactone 50 mg/day by Day 14. In this study, the percentage of subjects with a serum potassium in the range of 3.5 to 5.5 mEq/L at the end of the 8-week study treatment period was 90.5% (95% CI: 80.4%, 96.4%). The percentage of subjects with a serum potassium in this range by individual visits ranged from 91.2% to 100% and was 76.2% (95% CI: 63.8%, 86.0%) during the entire 8-week study treatment period. Although there was no control arm in this study, a higher incidence of hyperkalemia than that seen in the trial is expected in this population.

7 Review of Safety

A total of 791 subjects participated in clinical studies of RLY5016. Of these, 734 subjects (including patients with hyperkalemia, normokalemia, CKD, heart failure, diabetes, hypertension treated with RAASi, and/or who were receiving dialysis, and healthy volunteers) were exposed to at least one dose of RLY5016. In the pooled studies used to assess safety, a total of 584 subjects were exposed to RLY5016 for ≥ 4 weeks, 219 subjects were exposed for ≥ 6 months, and 149 subjects were exposed for ≥ 1 year.

The major safety concern with Veltassa is the potential for clinically important drug-drug interactions. Of the 28 compounds that underwent in vitro screening, seven (Amlodipine, Cinacalcet, Ciprofloxacin, Levothyroxine, Quinidine, Thiamine and Trimethoprim) showed > 50% binding to RLY5016 and another seven (Clopidogrel, Furosemide, Lithium, Metformin, Metoprolol, Verapamil and Warfarin) showed 30% to 50% binding. The Agency has asked the applicant to propose a pragmatic strategy to mitigate the potential risk of drug-drug interactions. The proposed strategy should be reasonably easy to implement and should be applicable to a wide variety of medications that are commonly used in the target population.

Interpretation of the safety database is limited by the lack of a control arm in many of the studies; however, the drug is not significantly absorbed and so a controlled safety database is perhaps less critical in this setting. In the clinical trials, drug-related adverse events (AEs) were primarily limited to GI effects and hypomagnesaemia. Constipation, hypomagnesaemia and diarrhea were the most common RLY5016-related AEs and were reported in 7.2%, 5.3%, and 4.8% of subjects respectively. Other common drug-related GI AEs included nausea (2.3%), flatulence (2.0%) and vomiting (1.8%). The majority of the GI AEs occurred early after starting treatment (within four weeks), were mild in severity, and resolved with continued treatment. While AEs of hypomagnesaemia were reported in approximately 5% of subjects, no subject developed a serum magnesium level less than 1.0 mEq/L and no subject discontinued treatment due to hypomagnesaemia. Of note, hypokalemia, a potential risk, was uncommon with the dosing regimen used in the phase 3 trial, which included titration based on response. The overall incidence of hypokalemia in the studies was 1.5%.

Fluoride is a degradation product of RLY5016 and so fluoride absorption resulting in accumulation of fluoride was a potential safety concern. Serum fluoride levels were evaluated at baseline and periodically in the clinically trials. In the pooled studies, mean increases in serum fluoride ranging from (b) (4) were observed at Weeks 1, 4, 8, 12 and the last measurement. There was no clear dose-response relationship. According to the published literature, serum fluoride levels (b) (4) may lead to adverse effects if such exposure is maintained over the long-term (i.e., months to years). In this context, the reported changes in fluoride levels seen in subjects on RLY5016 do not appear to be clinically meaningful. No fluoride accumulation related AEs were observed in a study of up to one year duration, however the size and the duration of the trial (as well as the lack of a control arm), limit interpretation of these data.

Because RLY5016 is a calcium-based potassium binder and calcium is exchanged with potassium in the colon lumen, RLY5016 has the potential to increase calcium absorption. Also, since calcium available in the gastrointestinal tract could complex with phosphate anions, RLY5016 could potentially decrease phosphate absorption. However, review of laboratory data did not suggest a clinically important effecton serum level of calcium or phosphate.

There were some differences in the incidence of drug-related AEs between the EU/US and non-EU countries. The reason is not clear. The integrity of the data at the non-EU sites that were audited has been confirmed by OSI.

In conclusion, the potential for drug-drug interactions remains a significant safety concern. Beyond this issue, no major safety concerns were identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety analyses focused on the data from 4 clinical studies conducted in patients with CKD and/or HF (see table 2 in Section 5.1). The clinical pharmacology studies summarized in the table below were also utilized in the safety evaluation.

Table 28: Summary of Clinical Pharmacology Studies Used to Evaluate Safety

Study Identifier	Location of CSR	Study Title and Objectives	Study Design and Type of Control	Dose (g/day) (Dosage Regimen)	N[a] (Active/ Placebo)	Population	Treatment Duration
RLY5016-101	Section 5.3.4.1	"A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Single and Multiple Dose Escalation Study to Evaluate the Safety and Tolerability of RLY5016 in Healthy Volunteers" • Assess the safety and tolerability of single and multiple doses	Double-blind, randomized, placebo-controlled, parallel arm, single and multiple dose	Fixed doses: 3, 15, 30, 60[b] (multiple dose phase, as divided doses TID)	33 (25/8)	Healthy subjects	8 days (multiple dose phase)
RLY5016-102	Section 5.3.4.1	"An Open-Label, Multiple-Dose Crossover Study to Evaluate the Pharmacology, Safety, and Tolerability of Three RLY5016 Dosing Regimens in Healthy Subjects" • Assess the pharmacologic effects of TID, BID, and QD dosing regimens	Open-label, randomized, multiple dose, crossover	Fixed dose: 30[b] (in TID, BID, QD regimens)	12 (12/0)	Healthy subjects	18 days
RLY5016-201	Section 5.3.4.2	"An Open-Label, Multiple Dose Study to Evaluate the Pharmacology, Safety, and Tolerability of RLY5016 in Hemodialysis Patients" • Assess the PD effects of RLY5016 on serum potassium in hyperkalemic subjects on hemodialysis	Open-label, single arm, multiple dose	Fixed dose: 15[b] (as divided dose TID)	6 (6/0)	Hemodialysis subjects	7 days

a. Includes all subjects enrolled in the study who received at least one dose of study drug.
b. Dose expressed as the amount of patiromer calcium (RLY5016).
c. Dose expressed as the amount of polymer anion (patiromer).
(Applicant's table from Summary of Clinical Pharmacology, table 2, Page 11)

7.1.2 Categorization of Adverse Events

Adverse events were coded according to MedDRA Version 16.0.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Four studies were pooled for the purpose of safety analyses. Two of these evaluated RLY5016 for the treatment of hyperkalemia and two evaluated RLY5016 for the prevention of hyperkalemia. In each of the pooled studies, subjects received RLY5016 for at least 28 days. Of note, these studies enrolled patients with underlying CKD and/or heart failure and studied dosing regimens relevant to labeling. The number of subjects treated, the treatment duration, and the mean daily dose in each trial is shown below. See also Section 5.1 for an overview of these studies.

- Study 301 (243 subjects; up to 12-week treatment duration; mean daily dose 18.2±6.6g)
- Study 205 (304 subjects; up to 52-weeks treatment duration; mean daily dose 26.3±9.3g)
- Study 202 (105 subjects; up to 4 weeks; mean daily dose 29.8±1.5g)
- Study 204 (63 subjects/8 weeks; mean daily dose 22.2 ± 7.6g)

Because of differences in study design, dose and/or population, the following studies were not pooled for the purpose of safety analyses:

- Study 101, a phase 1 placebo-controlled trial in 33 healthy subjects (duration of administration: 9 days)
- Study 102, a phase 1 open-label trial in 12 healthy subjects (duration of administration: 18 days)
- Study 103, a phase 1 open-label trial of time to onset of effect in 25 subjects with hyperkalemia and CKD (duration of treatment: 2 days)
- Study 201, a phase 2 open-label trial in 6 subjects with end-stage renal disease receiving dialysis and hyperkalemia (duration of treatment: 7 days).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall exposure: A total of 791 subjects, including patients with hyperkalemia, normokalemia, CKD, heart failure, diabetes, hypertension, and ESRD receiving dialysis, and also healthy volunteers, have participated in clinical studies of RLY5016. Of these, 734 subjects were exposed to at least one dose of RLY5016.

Pooled studies: 717 subjects were enrolled or randomized in Studies 202, 204, 205 and 301. Of these 717 subjects, 668 subjects were enrolled or randomized to RLY5016. A total of 49 subjects were treated with placebo only; another 52 subjects (out of the 668 subjects treated with RLY5016) were crossed over from RLY5016 to placebo. All of the subjects who were crossed over were enrolled in Study 301.

A total of 666 subjects received at least one dose of RLY5016 in the pooled studies and were included in the Overall RLY5016 group in the Safety Population. Two (2) subjects in the Treatment Studies were enrolled but not treated with RLY5016 and are therefore not included in the Safety Population. The overall extent of exposure for the pooled Safety Population is summarized in the table below. As shown in the table, a total of 584 subjects were exposed to RLY5016 for ≥ 4 weeks (1 month), 361 subjects were exposed for ≥ 8 weeks (2 months), 219 subjects were exposed for ≥ 6 months, and 149 subjects were exposed for ≥ 1 year. The long-term exposure data for RLY5016 are provided by Study 205, a 52-week treatment study.

Table 29: Overall Extent of Exposure in Pooled Studies (Safety Population)

Duration of Exposure	Number of Patients Exposed to RLY5016
0-4 weeks	666 (100%)
4-8 weeks	584 (87.7%)
8-12 weeks	361 (54.2%)
12 weeks to 6 months	282 (42.3%)
6 months to 9 months	219 (32.9%)
9-12 months	204 (30.6%)
≥ 12 months	149 (22.4%)

(Reviewer's table)

Demographic and baseline characteristics of subjects in the pooled studies: As shown in the table below, the majority of subjects treated with RLY5016 in the pooled studies were male, white, and ≥ 65 years of age.

Table 30: Demographic Characteristics of Subjects in the Pooled Studies (Safety Population)

Demographic Characteristics		
Age (years)	Mean	66.1±9.5
	Min, Max	29, 89
	< 65	268 (40.2%)
	≥ 65	398 (59.8%)
	≥ 75	132 (19.8)
Gender	Male	400 (60.1%)
Ethnicity	Not Hispanic or Latino	658 (98.8%)
Race*	African descent	4(0.6)
	Asian descent	1 (0.2%)
	Caucasian descent	660 (99.1)
	American Indian or Alaskan native	1 (0.2%)
	Native Hawaiian or Pacific Islander	0

(Reviewer's table)
*Race as captured on the CRF

Disease history, comorbidities, and concomitant medications: In the overall pooled population, most subjects had CKD, diabetes and hypertension, approximately half had heart failure, and almost one quarter reported a history of myocardial infarction. Information on concomitant

medications was collected beginning at screening and continued through the last follow-up visit. Data on disease history, comorbidities and concomitant medications are summarized in the following tables. The subjects enrolled in these studies represent the population at risk for hyperkalemia.

Table 31: Disease Status/History in Pooled Studies including Treatment Studies (Studies 205 and 301) and Prevention Studies (Studies 202 and 204)

	Treatment Studies	Prevention Studies	Overall
	RLY5016 FOS N = 547	RLY5016 FOS N = 119	RLY5016 FOS N = 666
Chronic Kidney Disease (CKD)			
Yes	547 (100%)	72 (60.5%)	619 (92.9%)
No	0	47 (39.5%)	47 (7.1%)
eGFR at Baseline (mL/min/1.73 m^2)[a]			
n	541	119	660
Mean (SD)	38.79 (17.272)	58.65 (22.862)	42.37 (19.910)
Q1, Q2, Q3	26.0, 36.0, 49.0	43.0, 54.0, 76.0	27.0, 40.0, 52.5
Min, Max	6.0, 100.0	14.0, 111.0	6.0, 111.0
CKD Stage (based on eGFR at Baseline; mL/min/1.73 m^2)			
≥ 90 (Stage 1)[b]	5 (0.9%)	2 (2.8%)	7 (1.1%)
60 – 89 (Stage 2)	55 (10.2%)	11 (15.3%)	66 (10.8%)
45 – 59 (Stage 3a)	132 (24.4%)	28 (38.9%)	160 (26.1%)
30 – 44 (Stage 3b)	159 (29.4%)	23 (31.9%)	182 (29.7%)
15 – 29 (Stage 4)	169 (31.2%)	7 (9.7%)	176 (28.7%)
< 15 (Stage 5)	21 (3.9%)	1 (1.4%)	22 (3.6%)
Serum Potassium at Baseline (mEq/L)[c]			
n	539	119	658
Mean (SD)	5.42 (0.459)	4.75 (0.479)	5.30 (0.529)
Q1, Q2, Q3	5.1, 5.4, 5.7	4.5, 4.7, 5.0	5.0, 5.3, 5.6
Min, Max	3.9, 9.4*	3.3, 6.1	3.3, 9.4*
< 5.1	93 (17.3%)	91 (76.5%)	184 (28.0%)
5.1 – < 5.5	221 (41.0%)	20 (16.8%)	241 (36.6%)
5.5 – < 6.0	174 (32.3%)	7 (5.9%)	181 (27.5%)
≥ 6.0	51 (9.5%)	1 (0.8%)	52 (7.9%)
Urine ACR at Baseline (mg/g)			
n	532	41	573
Mean (SD)	1017.7 (1729.49)	71.2 (162.10)	949.9 (1684.69)
Q1, Q2, Q3	30.5, 230.5, 1208.5	5, 12, 43	25, 184, 1083
Min, Max	3, 12324	3, 838	3, 12324
Diabetes Mellitus			
Yes	443 (81.0%)	46 (38.7%)	489 (73.4%)
No	104 (19.0%)	73 (61.3%)	177 (26.6%)
Hypertension			
Yes	540 (98.7%)	108 (90.8%)	648 (97.3%)
No	7 (1.3%)	11 (9.2%)	18 (2.7%)

Table 32: Disease Status/History in Pooled Studies including Treatment Studies (Studies 205 and 301) and Prevention Studies (Studies 202 and 204) (Cont'd)

	Treatment Studies	Prevention Studies	Overall
	RLY5016 FOS N = 547	RLY5016 FOS N = 119	RLY5016 FOS N = 666
Systolic Blood Pressure at Baseline (mmHg)[d]			
n	547	119	666
Mean (SD)	148.1 (16.08)	130.9 (15.24)	145.0 (17.23)
Q1, Q2, Q3	138, 149, 160	122, 130, 140	133, 145, 157
Min, Max	105, 197	98, 208	98, 208
Diastolic Blood Pressure at Baseline (mmHg)[d]			
n	547	119	666
Mean (SD)	81.2 (11.41)	80.1 (8.20)	81.0 (10.91)
Q1, Q2, Q3	73, 81, 90	78, 80, 85	73, 80, 88
Min, Max	48, 106	52, 105	48, 106
Heart Failure			
Yes	207 (37.8%)	119 (100%)	326 (48.9%)
No	340 (62.2%)	0	340 (51.1%)
NYHA Heart Failure Class at Baseline			
No heart failure diagnosis	340 (62.2%)	0	340 (51.1%)
I	45 (8.2%)	2 (1.7%)	47 (7.1%)
II	145 (26.5%)	58 (48.7%)	203 (30.5%)
III	17 (3.1%)	59 (49.6%)	76 (11.4%)
IV	0	0	0
Prior Myocardial Infarction			
Yes	115 (21.0%)	45 (37.8%)	160 (24.0%)
No	432 (79.0%)	74 (62.2%)	506 (76.0%)

Q1 = 25th percentile; Q2 = 50th percentile (median); Q3 = 75th percentile; SD = standard deviation

a. eGFR calculated using central laboratory data and the CKD-EPI equation
b. Subjects with eGFR ≥ 90 mL/min/1.73 m^2 may not have Stage 1 CKD. Patients with Stage 1 CKD and "normal eGFRs" (eGFR ≥ 90 mL/min/1.73 m2) are defined are defined by clinical practice guidelines as having urinary abnormalities, structural abnormalities or genetic traits that point to kidney disease . Thus subjects grouped in this category, in the absence of these findings, may not have CKD.
c. Serum potassium as determined by the central laboratory
d. The average of the three measurements collected at baseline in Studies 205 and 301
e. The baseline central laboratory serum potassium value of 9.4 mEq/L for Subject 301-190401 is erroneous. The subject's baseline average local laboratory serum potassium value was 5.45 mEq/L.

(Applicant's table, Summary of Safety, table 9, page 41)

Table 33: Concomitant Administration of RAASi Drugs in the Pooled ISS Studies

Study	Concomitant RAASi	
	Inclusion Criteria	RAASi as Study Treatment
Study 202	ACEI, ARB and/or BB, unless hyperkalemia caused discontinuation of these drugs in last 6 months	Spironolactone
Study 204	ACEI and/or ARB (and/or BB)	Spironolactone
Study 205	ACEI and/or ARB for at least 28 days prior to screening	Losartan with or without Spironolactone (Cohort 1) Spironolactone (Cohort 2)
Study 301	Stable dose of ACEI, ARB and/or AA for at least 28 days prior to screening	Not administered as a study treatment

(Applicant's table, Summary of Safety, table 10, page 44)

Reviewer comment: The size of the safety database and the duration of exposure seem reasonable for a product that is not significantly abosrobed.

7.2.2 Explorations for Dose Response

In the pooled studies, explorations for dose-response are confounded by a number of factors including different starting doses, the use of dose titration, different treatment durations, and different underlying diseases and comorbidities. Starting doses in some studies were based on subjects' screening serum potassium values; in these studies, subjects receiving higher starting doses because of higher screening serum potassium values may have had more severe underlying disease and burden of comorbid conditions, thus potentially confounding and limiting the interpretation of dose-response analyses.

Dose-relationship data are available from Study 205 in which subjects were randomized to 1 of 3 starting doses of RLY5016 for Oral Suspension within strata based on screening serum potassium (Stratum 1: 8.4, 16.8 and 25.2 g/day patiromer; Stratum 2: 16.8, 25.2 and 33.6 g/day patiromer). Despite the option for dose-titration at day 3, subjects in Study 205 remained close to their randomized doses throughout the duration of the study; therefore, data for these subjects may provide some information on potential dose-response relationships for safety/tolerability.

In Study 205, an association between higher starting doses of RLY5016 and increasing incidence of hypomagnesaemia AEs was observed (see table below). In addition, there was a greater incidence of constipation, hypokalemia and chronic renal failure in the highest dose group in comparison with the other dose groups. The increased incidence of chronic failure did not seem to be drug-related based on the narratives (see Section 7.3 for further discussion). No apparent relationships between higher starting doses and other AEs were noted in this study.

Table 34: Summary of Possible Dose related Treatment-Emergent Adverse Events in Study 205 (Safety Population)

	8.4 g/day N = 74 n (%)	**16.8 g/day N = 99 n (%)**	**25.2 g/day N = 101 n (%)**	**33.6 g/day N = 30 n (%)**
Subjects reporting at least 1TEAE	47 (63.5)	69 (69.7)	70 (69.3)	25 (83.3)
Constipation	4 (5.4)	5 (5.1)	5 (5.0)	5 (16.7)
Hypomagnesaemia	4 (5.4)	7 (7.1)	10 (9.9)	5 (16.7)
Hypokalemia	2 (2.7)	2 (2.0)	0 (0.0)	3 (10.0)
Chronic renal failure	5 (6.8)	9 (9.1)	7 (6.9)	7 (23.3)

(Reviewer table based on the CSR 205 report)

In Part A of the pivotal study, there was no apparent dose-related increase in the overall incidence of AEs. However, interpretation of these data is limited because doses were titrated.

In the un-pooled studies, the number of subjects with events of special interest was low. There was no clear evidence of a dose-response relationship in studies in healthy subjects that compared different fixed doses.

Reviewer's comment: Based on Study 205, hypomagnesaemia and constipation appear to be the two major dose-related adverse effects. Given the small number of subjects in the high dose group, estimates in this dose group are likely to be less reliable.

7.2.3 Special Animal and/or In Vitro Testing

Fluoride absorption was evaluated in a rat model and drug-drug interactions were evaluated via *in vitro* testing. The drug-drug interaction findings are summarized below; see Section 4.3 for information on fluoride absorption in animals.

Drug-drug interaction: A biologically-relevant *in vitro* test system was used to evaluate potential interactions between RLY5016S and a set of 28 orally administered compounds commonly used in the target patient population (Study RLY-TR-0130). The set of compounds tested included prototypical drugs from many drug classes, as well as vitamins and a hormone. Under the conditions of this *in vitro* study, drugs with > 50% binding included Amlodipine, Cinacalcet, Ciprofloxacin, Levothyroxine, Quinidine, Thiamin and Trimethoprim. Drugs with 30% to 50% binding included Clopidogrel, Furosemide, Lithium, Metformin, Metoprolol, Verapamil and Warfarin.

7.2.4 Routine Clinical Testing

Routine clinical testing included adverse event data collection and monitoring of laboratory parameters, vital signs, physical examinations and ECGs. Testing is considered to be adequate.

Given the nature of the product (i.e., its very low systemic absorption), a thorough QT study was not required or conducted.

7.2.5 Metabolic, Clearance, and Interaction Workup

Radiolabeled ADME studies were conducted in rats and dogs. These studies indicate that patiromer is not systemically absorbed and is excreted in the feces. Therefore, systemic PK studies were not performed in humans. As discussed in Sections 7.2.3, 7.5.5 and 4.4, *in vitro* studies were performed to evaluate RLY5016's potential to bind co-administered drugs. No *in vivo* drug-drug interactions studies were conducted.

The metabolic stability of the RLY5016 polymer was assessed ex vivo by measuring the cation content of polymer beads recovered from fecal samples obtained from subjects in a phase 1 study and comparing this content with the calcium content of the administered RLY5016 dose. The study showed no net overall cation accumulation or loss during passage through the human GI tract and a net binding and uptake of ~1 to 1.3 mEq of potassium per gram of drug administered. RLY5016 is considered to be metabolically stable and is not chemically changed during passage through the GI system. The physical stability of the RLY5016 beads during transit through the GI tract was assessed by the recovery of the product from fecal samples collected in the phase 1 study. The beads recovered from feces remained as intact spheres of approximately (b) (4) .

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Given the experience with sodium polystyrene sulfonate and other binders, potential safety concerns include GI tolerability and safety and drug-drug interactions. These issues are discussed elsewhere in this review. Sodium load is a concern with sodium polystyrene sulfonate, however, Veltassa does not use sodium as a counter-ion; hence Veltassa would not be expected to contribute to the sodium load in patients who use the product.

7.3 Major Safety Results

7.3.1 Deaths

A total of 20 deaths were reported in the drug development program including 18 deaths in subjects receiving RLY5016, 1 death in a subject who received 4 weeks of treatment with RLY5016 in Part A of Study 301 followed by placebo in Part B of the study, and 1 death in a subject treated with placebo only. These deaths occurred in the pooled studies. No subject deaths were reported in the unpooled studies/studies in healthy volunteers.

An independent Safety Review Board (SRB) adjudicated all deaths that occurred in the studies of RLY5016. The SRB reviewed all available clinical and laboratory data for each subject before providing a determination of the relationship of each death to either hyperkalemia or hypokalemia, and the adjudicated cause of death. The SRB assessed 19 subject deaths as unlikely related to hypo- or hyperkalemia (the relationship of one subject death to serum potassium could not be evaluated because no recent serum potassium values were available). No subject who died had a final study serum potassium value < 3.5 mEq/L; the last available on-study serum potassium values ranged from 49 days before the fatal event to the date of the fatal event. No subject who died had a final study serum magnesium value < 1.4 mg/dL. The last available on-study serum magnesium values ranged from 56 days before the fatal event to 1 day before the fatal event.

The major risk factors for death, particularly cardiovascular death, in the population included age ≥ 65 years, male gender, CKD, diabetes, heart failure, hypertension, and prior myocardial infarction. All 20 subjects who died had 4 or more of these risk factors, 9 subjects had 5 risk factors, 6 subjects had 6 risk factors, and 3 subjects had all 7 risk factors. These deaths are briefly summarized in the table below.

Table 35: Subject Listing of Fatal Events in All Studies

Study Subject Age (years) / Sex Country	Starting Dose and Last Dose Prior to Death	Fatal Event (Preferred Term) Verbatim Term SRB Cause of Death	Study Day / Days from Last Dose to Death	Baseline K^+ (Central lab) Baseline eGFR ($mL/min/1.73\ m^2$) Major Risk Factors[a]	SRB Relationship to Hypo - / Hyperkalemia Investigator Relationship to Study Treatment	Last Serum K^+ and Mg^{+2} Values (Day) Last Blood Pressure Value
202-504-101 70 / M Ukraine	Placebo	Sudden cardiac death *Death (sudden cardiac death)* Sudden cardiac death	9 / 0	K^+ 5.2 mEq/L eGFR 80.8 CKD, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 5.1 mEq/L (Day 7) Mg^{+2} 2.4 mg/dL (Day 7) 123/75 mmHg (Day 7)
204-1208 60 / M Georgia	16.8 g/day 42.0 g/day	Sudden death *Sudden death* Sudden cardiac death	61 / 5	K^+ 5.5 mEq/L eGFR 68.1 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.6 mEq/L (Day 56) Mg^{+2} 2.0 mg/dL (Day 56) 115/85 mmHg (Day 56)
204-2501 76 / F Slovenia	16.8 g/day 33.6 g/day	Sudden cardiac death *Sudden cardiac death* Sudden cardiac death	57 / 26	K^+ 5.1 mEq/L eGFR 30.2 CKD, DM, HF, HTN	Could not be determined [b] Not related	K^+ 5.1 mEq/L (Day 31) Mg^{+2} 2.3 mg/dL (Day 31) 105/75 mmHg (Day 31)
204-2508 60 / M Slovenia	16.8 g/day 16.8 g/day	Sudden cardiac death *Sudden cardiac death* Sudden cardiac death	29 / 1	K^+ 5.2 mEq/L eGFR 68.1 CKD, DM, HF, HTN	Unlikely / Unlikely Not related	K^+ 4.6 mEq/L (Day 28) Mg^{+2} 1.7 mg/dL (Day 28) 140/105 mmHg (Day 28)
205-20704 65 / M Croatia	16.8 g/day 16.8 g/day	Cholecystitis *Acute calculous cholecystitis* Acute myocardial infarction	372 / 42	K^+ 5.2 mEq/L eGFR 30.3 CKD, DM, HTN	Unlikely / Unlikely Not related	K^+ 3.5 mEq/L (Day 365) Mg^{+2} 1.92 mg/dL (Day 365) 128/76 mmHg (Day 365)
205-30105 56 / M Georgia	33.6 g/day 25.2 g/day	Sudden death *Sudden death* Sudden cardiac death	179 / 1	K^+ 5.8 mEq/L eGFR 55.8 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.3 mEq/L (Day 169) Mg^{+2} 2.07 mg/dL (Day 169) 98/66 mmHg (Day 169)
205-30124 62 / M Georgia	25.2 g/day 50.4 g/day	Sudden death *Sudden death* Sudden cardiac death	223 / 0	K^+ 5.7 mEq/L eGFR 37.0 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.5 mEq/L (Day 210) Mg^{+2} 1.58 mg/dL (Day 172) 116/81 mmHg (Day 210)
205-30323 66 / M Georgia	16.8 g/day 16.8 g/day	Sudden death *Sudden death* Sudden cardiac death	204 / 0	K^+ 5.7 mEq/L eGFR 47.8 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.7 mEq/L (Day 195) Mg^{+2} 2.21 mg/dL (Day 195) 132/87 mmHg (Day 195)
205-30324 70 / M Georgia	8.4 g/day 8.4 g/day	Diabetic vascular disorder *Diabetic angiopathy of left lower limb* Infection (Includes Sepsis)	41 / 3	K^+ 5.1 mEq/L eGFR 46.5 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.7 mEq/L (Day 36) Mg^{+2} 2.26 mg/dL (Day 29) 163/70 mmHg (Day 36)
205-30329 68 / M Georgia	16.8 g/day 25.2 g/day	Cerebrovascular accident *Stroke* Stroke not otherwise specified	96 / 4	K^+ 5.3 mEq/L eGFR 56.1 CKD, DM, HF, HTN, MI	Unlikely / Unlikely Not related	K^+ 4.8 mEq/L (Day 85) Mg^{+2} 2.19 mg/dL (Day 85) 125/80 mmHg (Day 85)
205-30515 60 / M Georgia	25.2 g/day 25.2 g/day	Sudden cardiac death *Sudden cardiovascular death* Acute myocardial infarction	23 / 1	K^+ 4.9 mEq/L eGFR 25.7 CKD, DM, HF, HTN	Unlikely / Unlikely Not related	K^+ 4.3 mEq/L (Day 22) Mg^{+2} 1.78 mg/dL (Day 15) 138/66 mmHg (Day 22)
205-30606 80 / F Georgia	25.2 g/day 25.2 g/day	Sudden death *Sudden death* Sudden cardiac death	233 / 1	K^+ 5.62 mEq/L (local lab) eGFR Not avail. CKD, DM, HF, HTN	Unlikely / Unlikely Not related	K^+ 5.3 mEq/L (Day 223) Mg^{+2} 3.19 mg/dL (Day 223) 114/68 mmHg (Day 223)
205-30607 76 / M Georgia	25.2 g/day 42.0 g/day	Mesenteric artery thrombosis *Mesenteric artery thrombosis* Gastrointestinal event	72 / 54	K^+ 6.3 mEq/L eGFR 31.5 (Screening) CKD, DM, HF, HTN	Unlikely / Unlikely Not related	K^+ 5.4 mEq/L (Day 23) Mg^{+2} 2.41 mg/dL (Day 16) 129/69 mmHg (Day 23)

Study Subject Age (years) / Sex Country	Starting Dose and Last Dose Prior to Death	Fatal Event (Preferred Term) Verbatim Term SRB Cause of Death	Study Day / Days from Last Dose to Death	Baseline K^+ (Central lab) Baseline eGFR (mL/min/ 1.73 m^2) Major Risk Factors	SRB Relationship to Hypo - / Hyperkalemia Investigator Relationship to Study Treatment	Last Serum K^+ and Mg^{+2} Values (Day) Last Blood Pressure Value
205-30815 73 / F Georgia	25.2 g/day 33.6 g/day	Brain death *Cerebrovascular death possibly caused by trauma* Neurological non-cardiovascular event	363 / 1	K^+ 5.1 mEq/L eGFR 40.8 CKD, DM, HTN	Unlikely / Unlikely Not related	K^+ 4.4 mEq/L (Day 338) Mg^{+2} 1.9 mg/dL (Day 338) 128/71 mmHg (Day 338)
205-51502 78 / M Hungary	25.2 g/day 8.4 g/day	Sudden death *Sudden death* Sudden cardiac death	246 / 1	K^+ 4.8 mEq/L eGFR 47.8 CKD, DM, HTN	Unlikely / Unlikely Not related	K^+ 5.0 mEq/L (Day 225) Mg^{+2} 1.85 mg/dL (Day 225) 116/79 mmHg (Day 225)
205-60103 58 / M Serbia	25.2 g/day 25.2 g/day	Myocardial infarction *Myocardial infarction* Acute myocardial infarction	13 / 1	K^+ 5.7 mEq/L eGFR 13.1 (Screening) CKD, DM, HF, HTN	Unlikely / Unlikely Not related	K^+ 4.8 mEq/L (Day 8) Mg^{+2} 2.31 mg/dL (Day 1) 204/91 mmHg (Day 8)
205-60213 66 / M Serbia	25.2 g/day 33.6 g/day	Sudden cardiac death *Sudden cardiovascular death* Sudden cardiac death	51 / 0	K^+ 5.2 mEq/L eGFR 88.7 (Screening) CKD, DM, HTN, MI x 2	Unlikely / Unlikely Not related	K^+ 4.5 mEq/L (Day 50) Mg^{+2} 1.85 mg/dL (Day 43) 150/93 mmHg (Day 50)
205-60413 65 / M Serbia	25.2 g/day 16.8 g/day	Myocardial infarction *Myocardial infarction* Acute myocardial infarction	181 / 13	K^+ 4.9 mEq/L eGFR 48.2 CKD, DM, HTN	Unlikely / Unlikely Not related	K^+ 4.7 mEq/L (Day 141) Mg^{+2} 1.53 mg/dL (Day 141) 190/91 mmHg (Day 141)
205-70310 60 / M Slovenia	25.2 g/day 25.2 g/day	Sudden cardiac death *Sudden cardiac death* Sudden cardiac death	210 / 1	K^+ 5.2 mEq/L eGFR 49.9 CKD, DM, HTN	Unlikely / Unlikely Not related	K^+ 4.6 mEq/L (Day 197) Mg^{+2} 1.78 mg/dL (Day 197) 143/72 mmHg (Day 197)
301-130505 74 / M Georgia	16.8 g/day Placebo	Thrombosis mesenteric vessel *Mesenteric thrombosis* Gastrointestinal event	67 / 4	K^+ 5.8 mEq/L eGFR 38.6 CKD, HF, MI	Unlikely / Unlikely Not related	K^+ 5.2 mEq/L (Day 63) Mg^{+2} 2.2 mg/dL (Day 63) 121/83 mmHg (Day 63)

a. Major risk factors include chronic kidney disease (CKD), diabetes mellitus (DM), heart failure (HF), hypertension (HTN) and myocardial infarction (MI).
b. Because no recent serum potassium value was available, the SRB could not assess the relationship between the fatal event and hypo- or hyperkalemia.

(Applicant's table, Summary of Clinical Safety, table 23, page 80)

Reviewer comments: I reviewed the narrative for all of the cases. As expected in this patient population, most deaths were related to cardiac disorders. Given the nature of the drug and lack of systemic absorption, there is no compelling reason to believe these deaths were causally related.

Based on the available data and SRB adjudication, no deaths appear to have been related to hyper/hypo-kalemia or hypomagnesaemia, however, since some laboratory data were evaluated more than a month (the last measurements of serum level of potassium and magenesium) before a patient's death, the possibility that hyper/hypo-kalemia or hypomagnesaemia played a role in some of the deaths cannot be entirely excluded. Monitoring of serum electrolytes should mitigate this risk in the post marketing setting.

7.3.2 Non-fatal Serious Adverse Events

In the pooled population, 8.3% of subjects reported at least one SAE. Cardiovascular events, renal events, and infection were the most common types of SAEs. Because this drug is not systemically absorbed, these SAEs are not likely to be drug-related, unless mediated in part by a drug-drug interaction. Based on the provided narratives of each SAE from all available studies, I did not identify any potential drug-related SAEs of concern in either short-term or long-term studies. SAEs appeared to be related to the subjects' underlying disease(s). There was no obvious relationship between SAEs and dose or treatment duration. There were no SAEs of

hypokalemia or hypomagnesaemia or GI SAEs that one might think could be causally related (e.g., obstruction). SAEs are summarized in the following table.

Table 36: Serious Adverse Events in Safety Population

Serious Adverse Events (SAEs)		Overall RLY 5016 population (n=666)
Total number of SAEs reported		79
Subject reporting at least one SAE		55 (8.3%)
Cardiac disorders	Total	16 (2.4%)
	Acute myocardial infarction	4 (0.6%)
	Atrial fibrillation	3 (0.5%)
	Cardiac failure	3 (0.5%)
	Myocardial infarction	3 (0.5%)
	Cardiac failure chronic	2 (0.3%)
	Coronary artery disease	2 (0.3%)
	Acute left ventricular failure	1 (0.2%)
	Angina pectoris	1 (0.2%)
	Atrioventricular block complete	1 (0.2%)
Renal and urinary disorders	Total	12 (1.8%)
	Renal failure chronic	7 (1.1%)
	Renal failure acute	3 (0.5%)
	Azotemia	1 (0.2%)
	Nephropathy toxic	1 (0.2%)
	Tubulointerstitial nephritis	1 (0.2%)
Infections and infestations	Total	8 (1.2%)
	Pneumonia	2 (0.3%)
	Urinary tract infection	2 (0.3%)
	Appendicitis	1 (0.2%)
	Arteriosclerotic gangrene	1 (0.2%)
	Endocarditis enterococcal	1 (0.2%)
	Escherichia bacteremia	1 (0.2%)
	Gastrointestinal infection	1 (0.2%)
	Staphylococcal sepsis	1 (0.2%)
	Subcutaneous abscess	1 (0.2%)
Metabolism and nutrition disorders	Total	5 (0.8%)
	Diabetes mellitus	1 (0.2%)
	Diabetes mellitus inadequate control	1 (0.2%)
	Gout	1 (0.2%)
	Hypoglycemia	1 (0.2%)
	Hypovolemia	1 (0.2%)
Vascular disorders	Total	5 (0.8%)
	Diabetic vascular disorder	2 (0.3%)
	Femoral artery occlusion	1 (0.2%)
	Hypertensive crisis	1 (0.2%)
	Hypotension	1 (0.2%)
Nervous system disorders	Total	4 (0.6%)
	Cerebrovascular accident	2 (0.3%)
	Ischemic stroke	2 (0.3%)
	Transient ischemic attack	1 (0.2%)
Gastrointestinal disorders	Total	3 (0.5%)
	Gastric ulcer	1 (0.2%)
	Gastric ulcer hemorrhage	1 (0.2%)

	Mesenteric artery thrombosis	1 (0.2%)
Investigations	Total	2 (0.3%)
	Anticoagulation drug level below therapeutic	1 (0.2%)
	Intraocular pressure increased	1 (0.2%)
Eye disorders	Diabetic retinopathy	1 (0.2%)
Hepatobiliary disorders	Cholecystitis	1 (0.2%)
Neoplasms	Colon cancer	1 (0.2%)

(Reviewer's table)

7.3.3 Dropouts and/or Discontinuations

Overall, AEs that led to permanent discontinuation of RLY5016 occurred in 49 (7.4%) subjects in the pooled studies. Gastrointestinal AEs were the most common class of AEs leading to withdrawal in subjects treated with RLY5016 and placebo. Most of the GI adverse events that led to permanent discontinuation of RLY5016 occurred in the first 4 weeks of treatment. Other events occurred in a larger percentage of subjects over time, which is expected with a longer duration of follow-up, and were not considered by the investigator to be drug-related. These data are summarized in the following tables.

Table 37: Adverse Events Leading to Discontinuation of RLY5016 in the Pooled Studies

	Number of subjects
Total*	49 (7.4%)
Study 301- Part A	12 (4.9%)
Study 205	28 (9.2%)
Study 204	5 (6.3%)
Study 202	4 (7.1%, RLY5016) vs. 3 (6.1%, placebo)

(Reviewer's table)
*Total is for AEs leading to permanent discontinuation of RLY5016.

Table 38: Adverse Events Leading to Permanent Discontinuation in > 1 Subject Treated with RLY5016 by Time Period (Safety Population)

Adverse events leading to discontinuation		Overall RLY5016 FOS (n = 666)		
		Through Week 4	Through Week 8	Through Week 12
Subjects reporting at least one AE leading to discontinuation		30 (4.5%)	40 (6.0%)	41 (6.2%)
Gastrointestinal Disorders	Total	15 (2.3%)	16 (2.4%)	16 (2.4%)
	Vomiting	4 (0.6%)	5 (0.8%)	5 (0.8%)
	Diarrhea	4 (0.6%)	4 (0.6%)	4 (0.6%)
	Flatulence	3 (0.5%)	3 (0.5%)	3 (0.5%)
	Constipation	2 (0.3%)	2 (0.3%)	2 (0.3%)
Renal and urinary disorders	Total	5 (0.8%)	10 (1.5%)	10 (1.5%)
	Renal failure chronic	4 (0.6%)	8 (1.2%)	8 (1.2%)
	Renal failure acute	1 (0.2%)	2 (0.3%)	2 (0.3%)
Metabolism and nutrition disorders	Total	3 (0.5%)	5 (0.8%)	5 (0.8%)
	Hypokalemia	2 (0.3%)	3 (0.5%)	3 (0.5%)
Cardiac disorders[1]		2 (0.3%)	3 (0.5%)	3 (0.5%)
Immune system disorders[2]		2 (0.3%)	2 (0.3%)	2 (0.3%)
Vascular disorders[3]		1 (0.2%)	2 (0.3%)	2 (0.3%)

1: Atrial fibrillation; myocardial infarction; 2: Allergic edema, hypersensitivity ; 3: Hypertensive crisis
(Reviewer's table)

7.3.4 Significant Adverse Events

As discussed above, GI AEs were the the main reason for discontinuation of therapy for an AE. However, in general, GI AEs were mild, reversible and tolerated.

7.3.5 Submission Specific Primary Safety Concerns

As this product is not significantly absorbed, primary safety concerns include GI events, hypokalemia, hypomagnesaemia, the potential for accumulation of fluoride which can be released from the RLY5016 (b) (4) and interactions with other commonly used drugs. GI events are discussed below; see Section 7.2.3 for information on drug-drug interactions and Section 7.4.2 for discussion of the other safey concerns.

Gastrointestinal events were among the most common AEs in subjects treated with RLY5016. In the 666 subjects treated with RLY5016, the most common gastrointestinal events were constipation (7.2% of subjects) and diarrhea (4.8% of subjects). The median duration of the first constipation event was 9.5 days (interquartile range: 5 to 15.5 days) and the median duration of the first diarrhea event was 2 days (interquartile range: 2 to 4 days). Gastrointestinal AEs typically occurred within the first 4 weeks of treatment with RLY5016. Between weeks 4 and 12, there was no clinically meaningful increase in gastrointestinal AEs in subjects treated with RLY5016. In the pooled studies, five of 666 subjects (0.8%) had severe gastrointestinal events including: one subject with mesenteric artery thrombosis attributed to atrial filbration without anticoagulant; one subject with a gastric ulcer attributed to concomitant medications

acetylsalicylic acid and tramadol with paracetamol; one subject with gastric ulcer hemorrhage attribued to acute stress following cholecystectomy; and two subjects with non-serious, severe flatulence (these subjects did not discontinue RLY5016). Eighteen of 666 subjects (2.7%) discontinued treatment because of gastrointestinal AEs including vomiting (5, 0.8%), diarrhea (4, 0.6%), constipation (3, 0.5%), and flatulence (3, 0.5%).

In Study 202, 12 of 56 subjects (21.4%) in the RLY5016 group and 3 of 49 subjects (6.1%) in the placebo group had gastrointestinal AEs. No subject in Study 202 had a serious gastrointestinal event. A severe gastrointestinal event was reported by one subject in the RLY5016 (flatulence) group. Two of 56 subjects (3.6%) in the RLY5016 group and one of 49 subjects (2.0%) in the placebo group had a gastrointestinal AE that led to permanent discontinuation of study drug. The gastrointestinal events that led to permanent discontinuation of study drug in the RLY5016 group were flatulence and vomiting, and in the placebo group were diarrhea and fecal incontinence.

In the un-pooled studies of RLY5016, as in the pooled studies, gastrointestinal AEs were the most common events. However, none of these events was severe or serious, and none led to discontinuation of study drug.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the pooled safety population, the common AEs were constipation (7.2%), hypomagnesaemia (5.3%), renal failure chronic (5.4%), diarrhea (4.8%), hypertension (4.7%), anemia (2.7%), headache (2.6%), hyperglycemia and nausea (2.3% each), and abdominal discomfort, flatulence, hypoglycemia, edema peripheral, supraventricular extrasystoles and ventricular extrasystoles (2.0% each). Data are provided in the table below.

Table 39: Common Adverse Events Occurring in ≥ 2% of Subjects Treated with RLY5016 (Safety Population)

Common AEs		Total number of subjects (N =666)
Subjects with any adverse events		405 (60.8%)
Gastrointestinal disorders	Constipation	48 (7.2%)
	Diarrhea	32 (4.8%)
	Nausea	15 (2.3%)
	Abdominal discomfort	13 (2.0%)
	Flatulence	13 (2.0%)
Renal and urinary disorders	Chronic renal failure	36 (5.4%)
Metabolism and nutrition disorders	Hypomagnesaemia	35 (5.3%)
	Hyperglycemia	15 (2.3%)
	Hypoglycemia	13 (2.0%)
Vascular disorders	Hypertension	31 (4.7%)
Blood and lymphatic system disorders	Anemia	18 (2.7%)
Nervous system disorders	Headache	17 (2.6%)
Cardiac disorders	Ventricular extrasystoles	13 (2.0%)
	Supraventricular extrasystoles	13 (2.0%)
General disorders and administration site conditions	Edema peripheral	13 (2.0%)

(Reviewer's table)

In Study 202, the percentage of subjects with one or more AEs was greater in the RLY5016 group than in the placebo group (51.8% vs. 28.6%). The most common AEs in subjects treated with RLY5016 were flatulence (7.1%) and constipation, diarrhea and blood urea increased (5.4% each); in the placebo group, no individual AE was reported in > 2 subjects as shown in the table below.

Table 40: Adverse Events Reported in 2 or More Subjects in Study 202 (Safety Analysis Set)

System Organ Class Preferred Term	Treatment Group		Total
	RLY5016 FOS 30 g/day (N = 56)	Placebo (N = 49)	(N = 105)
Subjects With at Least One AE	29 (51.8%)	14 (28.6%)	43 (41%)
Gastrointestinal disorders	12 (21.4%)	3 (6.1%)	15 (14.3%)
Flatulence	4 (7.1%)	0	4 (3.8%)
Constipation	3 (5.4%)	0	3 (2.9%)
Diarrhoea	3 (5.4%)	1 (2.0%)	4 (3.8%)
Vomiting	2 (3.6%)	0	2 (1.9%)
Cardiac disorders	4 (7.1%)	1 (2.0%)	5 (4.8%)
Coronary Artery Disease	2 (3.6%)	0	2 (1.9%)
Supraventricular Extrasystoles	2 (3.6%)	1 (2.0%)	3 (2.9%)
Investigations	4 (7.1%)	2 (4.1%)	6 (5.7%)
Blood Urea Increased	3 (5.4%)	0	3 (2.9%)
Nervous system disorders	4 (7.1%)	1 (2.0%)	5 (4.8%)
Headache	2 (3.6%)	0	2 (1.9%)
General disorders and administration site conditions	3 (5.4%)	1 (2.0%)	4 (3.8%)
Oedema Peripheral	2 (3.6%)	0	2 (1.9%)
Metabolism and nutrition disorders	3 (5.1%)	2 (4.1%)	5 (4.8%)
Diabetes Mellitus	2 (3.6%)	0	2 (1.9%)
Gout	1 (1.8%)	1 (2.0%)	2 (1.9%)
Renal and urinary disorders	1 (1.8%)	4 (8.2%)	5 (4.8%)
Renal Failure Acute	1 (1.8%)	1 (2.0%)	2 (1.9%)
Renal Impairment	0	2 (4.1%)	2 (1.9%)
Vascular disorders	0	2 (4.1%)	2 (1.9%)
Hypotension	0	2 (4.1%)	2 (1.9%)

(Applicant's table from Study 202 CSR, Table 14.3.4)

In the un-pooled studies, many of the common events were similar to those observed in the pooled studies as summarized below:

- In Study 101, the most common AEs in the 25 subjects in the RLY5016 group were flatulence (16%), skin irritation (16%; all assessed by the investigator as due to the adhesive on ECG leads), abnormal dreams (8%), alanine aminotransferase increased (8%; this event was also common in subjects in the placebo group), diarrhea (8%) and headache (8%). The common AEs in the 8 subjects in the placebo group were similar to those observed in subjects treated with RLY5016, and included flatulence (25%), headache (25%), alanine aminotransferase increased (12.5%) and diarrhea (12.5%).
- In Study 102, the most frequently-reported AEs were abdominal pain, constipation, flatulence, vomiting, headache, and skin irritation (due to adhesive on ECG leads). Each of these events was reported in 1 of the 12 subjects (8%) treated with RLY5016.

- In Study 103, the most common AEs (and the only events occurring in more than 1 subject) were constipation and hypotension, which each occurred in 2 of 25 subjects (8%).
- In Study 201, the only AEs that occurred during the treatment period were nausea, abdominal rigidity, and furuncle. Each of these events occurred in 1 of the 6 study subjects (17%) treated with RLY5016.

7.4.2 Laboratory Findings

Hematology: In the pooled studies, most subjects treated with RLY5016 had normal hematology parameter values at baseline, and for most subjects, hematology values remained within the normal range during study treatment. There were no clinically meaningful changes in any hematology parameters including hemoglobin, hematocrit, erythrocyte, platelet or leukocyte counts.

In Study 202, changes from baseline in hematology parameters were minimal and similar between the RLY5016 and placebo groups.

In un-pooled Studies 101, 102, 103 and 201, no clinically meaningful changes in hematology parameters were observed, and no subject had an AE related to an abnormality in a hematology parameter.

Clinical chemistry: Clinical chemistry parameters including potassium, magnesium, calcium, phosphate, fluoride, BUN/creatinine and hepatic enzymes are discussed below.

Potassium: Of the 663 subjects in the Overall RLY5016 group with data for this analysis, 31 subjects (4.7%) had a treatment-emergent serum potassium value < 3.5 mEq/L. Two of these subjects had a serum potassium value < 3.5 mEq/L post-treatment; no subject had a treatment-emergent, on-study serum potassium value < 3.0 mEq/L. Of the 29 subjects with a serum potassium value < 3.5mEq/L, 11 were female and 18 were male. Twenty of the 29 subjects were ≥ 65 years of age. Four of the 29 subjects had an increase in RLY5016 dose in the 2 weeks preceding the serum potassium value < 3.5 mEq/L. Most subjects had no concurrent AEs; however, 3 subjects had gastrointestinal AEs, including diarrhea, frequent hard stools, and an unspecified gastrointestinal infection; diarrhea or a gastrointestinal infection (if associated with diarrhea) could have contributed to the loss of potassium in the stool. No subject reported a concomitant neuromuscular or muscle weakness AE.

No subject death was attributed to serum potassium. No subject in the pooled or un-pooled studies had an SAE of hypokalemia or hyperkalemia. Six subjects (0.9%) in the overall RLY5016 group discontinued from the studies because of hypokalemia events which were considered to be RLY5016-related. In addition, in the pooled studies, subjects with low serum potassium values that met protocol-specified withdrawal criteria were to be permanently withdrawn from the study. A total of 11 subjects treated with RLY5016, including 2 subjects in Study 202, 7 subjects in Study 205, and 2 subjects in Study 301 were withdrawn because of meeting the protocol-specified withdrawal criteria (See section 5). In the un-pooled Studies 102,

103 and 201, no subject treated with RLY5016 had a treatment-emergent serum potassium value < 3.5 mEq/L. In un-pooled Study 101, one subject had a serum potassium value of 3.4 mEq/L.

Magnesium: In the Overall RLY5016 group, at Weeks 1, 4, 8, 12 and last on-study measurement, there was a slight decrease from baseline in mean serum magnesium values that ranged from 0.119 to 0.172 mg/dL with the greatest decrease occurring at Week 1. The last on-study mean change from baseline was -0.162 mg/dL. Overall, the proportion of subjects in the Overall RLY5016 group with serum magnesium values < 1.4 mg/dL, < 1.2 mg/dL, and < 1.0 mg/dL at any time point was 9.3%, 2.0% and 0%, respectively.

- Magnesium-related AEs: Of the 20 subjects who died during participation in the studies of RLY5016, no subject had a last study serum magnesium value of < 1.4 mg/dL. No subject in the pooled studies of RLY5016 had a SAE of hypomagnesaemia or permanently discontinued treatment with RLY5016 because of an AE of hypomagnesaemia. In the 666 subjects in the overall RLY5016 group, hypomagnesaemia as an AE was reported in 35 subjects (5.3%) and the AE of blood magnesium decreased was reported in 5 subjects (0.8%).
- Analysis of serum level of magnesium < 1.2 mg/dl: Twelve subjects (1.9%) had serum magnesium values < 1.2 mg/dL as their lowest post-baseline value after having had a normal or high value at baseline. No subject had a serum magnesium value < 1.0 mg/dL. A time to event analysis of the first serum magnesium value < 1.2 mg/dL in the pooled Safety Population showed that events occurred over time, with no clustering at a particular time point. No clear relationship between daily dose at onset of serum magnesium values < 1.2 mg/dL or mean daily dose of RLY5016 and occurrence of serum magnesium values < 1.2 mg/dL was observed. The percentage of subjects with serum magnesium values < 1.2 mg/dL was greater in the group with baseline eGFR values ≥ 30 mL/min/1.73 m^2 (1.4%) than in those with baseline eGFR values < 30 mL/min/1.73 m^2 (0.5%).
- Analysis of serum magnesium in the placebo-control study: In Study 202, individual serum magnesium values were below the lower limit of normal (i.e., < 1.8 mg/dL) in 13 of 53 subjects (24.5%) treated with RLY5016 and 1 of 47 subjects (2.1%) treated with placebo (p = 0.001). The relatively high proportion of subjects in the RLY5016 group with serum magnesium values < 1.8 mg/dL may be related to the relatively high fixed dose of RLY5016, 25.2 g/day patiromer in this study. In the un-pooled Studies 101, 102, 103 and 201, no subject had a serum magnesium value < 1.2 mg/dL.
- Magnesium supplementation: An evaluation of magnesium supplementation use was performed in Study 205. In Stratum 1 (baseline serum potassium 5.0 to ≤ 5.5 mEq/L), 16.3% of subjects were taking magnesium compounds at baseline as compared to 16.8% during the study. In Stratum 2 (baseline serum potassium > 5.5 to 6.0 mEq/L), 19% of subjectswere taking magnesium compounds at baseline as compared to 21.4% during the study. In subjects who received magnesium supplements while treatment with RLY5016 was continuing, serum magnesium levels generally increased relative to pre-magnesium supplement values.

Calcium and phosphate: RLY5016 has the potential to increase calcium absorption, as calcium ions are exchanged with potassium ions. Also, as calcium available in the gastrointestinal tract could complex with phosphate anions, RLY5016 could potentially decrease phosphate absorption.

At Weeks 1, 4, 8 and 12 and the last measurement, mean calcium and phosphate values fluctuated around the baseline mean value and no trend was observed. In the pooled studies, the serum levels of calcium and phosphate in most subjects remained within the normal range during study treatment at Weeks 1, 4, 8 and 12. Twenty of 655 subjects (3.0%) had treatment-emergent serum calcium values > 11 mg/dL, and 61 subjects (9.3%) had treatment emergent serum calcium values < 8.0 mg/dL. Seventeen of 655 subjects (2.6%) had treatment-emergent phosphate values < 2.0 mg/dL. No subject in the pooled clinical studies of RLY5016 had a hypercalcemia or hypophosphatemia SAE, and no subject discontinued from the studies because of a calcium- or phosphate-related AE. There were two AEs of hypocalcemia, one AE of hypercalcemia, one AE of hyperphosphatemia and no hypophosphatemia AE.

In Study 202, there were no clinically significant changes from baseline or differences between the RLY5016 and placebo groups in serum calcium values. There was a slight decrease in serum phosphate values from baseline in the treatment group but not in the placebo group.

In the un-pooled studies, a dose-related increase from baseline in the mean daily urinary calcium excretion value was observed in Study 101. The mean dietary calcium intake was similar among the dose groups. Conversely, a dose-related decrease from baseline in the mean daily urinary phosphate excretion value was observed. In un-pooled Studies 101, 102, 103 and 201, there were no signals related to serum calcium or phosphate values, and no subjects had clinically important abnormalities in these parameters.

Mean changes in serum levels of potassium, magnesium, calcium and phosphate are summarized in the tables below.

Table 41: Summary of Mean Changes from Baseline to Last Measurement while on RLY5016, Selected Serum Analytes (Safety Population)

Analyte	Treatment Studies RLY5016 FOS N = 547	Prevention Studies RLY5016 FOS N = 119	Overall RLY5016 FOS N = 666
Potassium (mEq/L)			
Baseline Mean (SD)	n = 539	n = 119	n = 658
	5.42 (0.459)	4.75 (0.479)	5.30 (0.529)
Mean (SD) Change from Baseline at Last On-drug Measurement	n = 533	n = 118	n = 651
	-0.83 (0.690)	-0.22 (0.640)	-0.72 (0.719)
Magnesium (mg/dL)			
Baseline Mean (SD)	n = 541	n = 119	n = 660
	2.091 (0.2929)	2.355 (0.2974)	2.139 (0.3107)
Mean (SD) Change from Baseline at Last On-drug Measurement	n = 524	n = 116	n = 640
	-0.152 (0.2846)	-0.207 (0.2858)	-0.162 (0.2854)
Calcium (mg/dL)			
Baseline Mean (SD)	n = 541	n = 119	n = 660
	9.33 (0.635)	8.97 (0.448)	9.27 (0.621)
Mean (SD) Change from Baseline at Last On-drug Measurement	n = 524	n = 116	n = 640
	0.06 (0.605)	-0.00 (0.373)	0.05 (0.570)
Phosphate (mg/dL)			
Baseline Mean (SD)	n = 537	n = 119	n = 656
	3.78 (0.691)	3.54 (0.602)	3.73 (0.681)
Mean (SD) Change from Baseline at Last On-drug Measurement	n = 520	n = 116	n = 636
	-0.09 (0.777)	-0.02 (0.864)	-0.08 (0.793)

(Applicant's table from Summary of Clinical Safety, table 33 page 124)

Table 42: Summary of Changes from Baseline in Selected Serum Analytes in Study 202 (Safety Analysis Set)

Analyte	RLY5016 for Oral Suspension		Placebo		*P*-value (RLY5016 FOS vs. Placebo)
	Mean (SD) Baseline Value	LS Mean (SEM) Change from Baseline to Last On-Treatment Time Point	Mean (SD) Baseline Value	LS Mean (SEM) Change from Baseline to the Last On-Treatment Time Point	
	(N = 55[a])		(N = 49[a])		
Potassium[d] (mEq/L)	4.71 (0.45)	-0.21	4.68 (0.40)	0.23	< 0.001
	(N = 53[b])		(N = 47[c])		
Magnesium (mg/dL)	2.32 (0.29)	-0.23 (0.03)	2.33 (0.26)	0.02 (0.04)	< 0.001
Calcium (mg/dL)	8.85 (0.44)	0.04 (0.05)	8.89 (0.39)	-0.04 (0.05)	0.276
Phosphate (mg/dL)	3.53 (0.62)	-0.15 (0.14)	3.49 (0.48)	0.33 (0.15)	0.019

a. The number of subjects with a baseline and Day 28 value
b. The N at baseline was 56 for all parameters listed and was 53 at the final time point.
c. The N at baseline was 49 for all parameters listed and was 47 at the final time point for all parameters listed except for serum phosphate (N = 46).
d. The endpoint value was the last assessment value while on study drug or within 1 day after taking the last dose of study drug.

(Applicant's table from Summary of Clinical Safety, table 34 page 125)

Fluoride: In the pooled studies, mean increases in serum fluoride ranging from (b) (4) were observed at Weeks 1, 4, 8, 12 and the last measurement. No clear dose relationship was observed between the mean serum fluoride values or changes from baseline and the mean daily dose or the total dose of RLY5016, except that an increase in the mean value for last on-study serum fluoride measurements with increasing dose of RLY5016 was observed in subjects with baseline serum potassium values < 5.5 mEq/L, and in the highest dose group for subjects with baseline serum potassium values > 5.5 mEq/L. In subjects treated with RLY5016, no pattern of change from baseline in serum fluoride values was observed by CKD stage (i.e., ≤ Stage 2, Stage 3a, Stage 3b, and Stage 4/5). The maximum median increase from baseline in serum fluoride values was (b) (4) at Week 8 in subjects with Stage ≤ 2 CKD, (b) (4) at Week 8 for subjects with Stage 3a CKD, 6.5 ng/mL at Week 8 for subjects with Stage 3b CKD, and (b) (4) at Week 1 for subjects with Stage 4 or 5 CKD.

No AEs related to serum fluoride values were reported for subjects in the pooled clinical studies of RLY5016. Of the 666 subjects in the Overall RLY5016 group, fluoride data are available for 643 subjects. Of these 643 subjects, 50 subjects (7.8%) had treatment-emergent serum fluoride values of (b) (4) The highest value reported was (b) (4); the subject's prescribed dose at the time of this value was 0 g/day patiromer. For subjects in the overall RLY5016 group, there were a total of (b) (4) post-baseline fluoride values. Of these, 57 values (3.9%) were (b) (4) Two subjects treated with RLY5016 reported fractures. Subject 205-20104 had a clavicle fracture on Day 132 while receiving RLY5016 at a dose of 50.4 g/day patiromer. The subject's serum fluoride value at baseline (Day 1) was (b) (4); thereafter the subject's serum fluoride values remained (b) (4) through Day 142. Subject 205-70305 had a patella fracture on Day 168 while receiving 8.4 g/day patiromer; this subject did not have a serum fluoride value (b) (4) at any study assessment. Therefore, these two cases of bone fracture do not appear to be fluoride-related.

In Study 202, small mean increases from baseline of (b) (4), at days 14 and 28, respectively, were observed in the RLY5016 group. In the placebo group, slight decreases from baseline in mean serum fluoride levels were observed. The small observed increase in serum fluoride level in subjects treated with RLY5016 was not considered clinically meaningful. In un-pooled Study 101, pharmacokinetic parameter estimates of Cmax and Tmax for serum fluoride on Days 1, 16, 19 and overall were calculated. Median Cmax after repeated (b) (4) times daily administration increased in proportion to increasing dose of RLY5016, with median maximum values ranging from (b) (4) in the lowest dose group (b) (4) in the highest dose group (b) (4) The highest observed serum fluoride concentrations during the multiple-dose study period were observed, on average, between 4 and 7 days of initiation of treatment with RLY5016. In un-pooled Studies 102 and 201, small, clinically insignificant increases in serum fluoride were observed in subjects who received RLY5016. In Study 103, serum fluoride was not measured because the duration of study treatment was too brief to allow for meaningful analyses of changes from baseline.

Mean values of serum fluoride during treatment are summarized in the following table.

Table 43: Mean Values of Serum Fluoride in Pooled Studies (Safety Population)

Treatment	Serum level of Fluoride (ng/mL)					
	Baseline	Week1	Week 4	Week 8	Week 12	Last measure
RLY 5016						(b) (4)
Placebo						

(Reviewer's table)

Reviewer comments: There is an increase in serum fluoride during RLY5016 treatment. According to the published literature, serum fluoride levels (b) (4) *may lead to adverse effects if such exposure is maintained over the long-term (i.e., months to years). Hence, the increase caused by RLY5016 appears to be mild and would not be expected to be clinically meaningful.*

Creatinine and BUN: Overall, there were no clinically meaningful changes from baseline values. There were a few adverse events of acute kidney injury and CKD (see tables in Sections 7.3.2, 7.3.3, and 7.4.1). Based on the provided narratives, these cases did not appear to be treatment related.

Hepatic enzymes: There were no clinically meaningful changes from baseline values.

There were no other obvious drug-related findings in laboratory examinations.

7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs other than the changes in blood pressure discussed below.

Overall, patients appeared to have poor blood pressure control at baseline, and decreases in blood pressure were observed in subjects treated with RLY5016 in the pooled studies. The magnitude of this effect was greater in the subjects with elevated systolic and diastolic blood pressures at baseline. These changes may be related to an increase in the antihypertensive medication dose, addition of new antihypertensive medication, closer monitoring, or potentially to an indirect effect of potassium-lowering on serum aldosterone levels.

7.4.4 Electrocardiograms (ECGs)

In subjects treated with RLY5016 in the pooled studies, at Weeks 1, 4, 8 and 12 and the last study measurement, there were small fluctuations around the baseline mean value for the parameters heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval; no obvious trends were observed. Results are briefly summarized below.

- QTcF changes: Of the 525 subjects in the Overall RLY5016 for Oral Suspension group with baseline QTcF intervals ≤ 450 msec, 132 subjects (25.1%) had a post-baseline ECG with a QTcF interval of > 450 msec and 43 subjects (8.2%) had a post-baseline ECG with a QTcF interval > 470 msec. Six (6) subjects (1.1%) had a post-baseline ECG with a QTcF interval of

> 500 msec. A total of 42 subjects (6.9%) in the Overall RLY5016 group had increases from baseline in QTcF interval of > 60 msec and a total of 164 subjects (26.9%) had increases > 30 msec. The proportions of subjects with increases in QTcF intervals of > 30 msec and > 60 msec increased from Week 1 to Week 12.

- Long PR and QRS intervals: The proportions of subjects with long PR and QRS intervals were similar at baseline, Weeks 1, 4, 8 and 12, and at the last study observation. A total of 27.4% of subjects had post-baseline PR intervals > 200 msec and 25.2% of subjects had post-baseline QRS intervals > 120 msec at any time while on-study.
- No subject in Study 103 or 301 had an abnormal ECG finding that was assessed by the SRB (safety review board) as related to hypokalemia. Three subjects in Study 301 and no subject in Study 103, had post-treatment ECG abnormalities assessed by the SRB as related to hyperkalemia. Only one of these subjects had an AE concurrent with the ECG abnormality, and this event was hyperkalemia.

In the non-pooled studies including Studies 101, 102 and 201, no clinically significant changes from baseline were observed in mean RR, QT, or QTcB intervals after TID, BID, and QD dosing of RLY5016, and no subject had an AE related to an ECG finding.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

RLY5016 is a small molecule that is not significantly absorbed. Therefore, it is not expected to have immunogenic potential. Neither the non-clinical studies nor the clinical studies suggest an increase in adverse events of potential immunogenic etiology.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In Study 205, subjects were randomized to 1 of 3 starting doses of RLY5016 based on screening serum potassium (Stratum 1: 8.4, 16.8 and 25.2 g/day patiromer; Stratum 2: 16.8, 25.2 and 33.6 g/day patiromer). Despite the option for dose-titration, subjects in this study remained close to their randomized doses throughout the duration of the study. In Study 205, an association between higher starting doses of RLY5016 and an increased incidence of the AE hypomagnesaemia was observed. Relative to the other starting dose groups, the incidence of constipation was also greater in subjects randomized to the highest starting dose. No apparent relationships between higher starting doses and other AEs were noted in this study. The overall incidence of AEs was higher in the group of subjects randomized to a starting dose of 33.6 g/day patiromer; however, the number of subjects treated with this starting dose of RLY5016 was small. Data are summarized in the table below.

Table 44: Summary of Treatment-Emergent Adverse Events in ≥5.0% of Subjects in Any One Starting Dose Group in Study 205 (Safety Population)

TEAEs		RLY5016 Starting Dose (g/day patiromer)			
		8.4 N=74 n (%)	16.8 N=99 n (%)	25.2 N=101 n (%)	33.6 N=30 n (%)
Gastrointestinal disorders	**Constipation**	4 (5.4)	5 (5.1)	5 (5.0)	5 (16.7)
	Diarrhea	6 (8.1)	8 (8.1)	2 (2.0)	1 (3.3)
Metabolism and nutrition disorders	Hypokalemia	2 (2.7)	2 (2.0)	0 (0.0)	3 (10.0)
	Hypomagnesaemia	4 (5.4)	7 (7.1)	10 (9.9)	5 (16.7)
	Hypoglycemia	1 (1.4)	4 (4.0)	2 (2.0)	3 (10.0)
Cardiac disorders	Ventricular extrasystoles	2 (2.7)	4 (4.0)	3 (3.0)	2 (6.7)
Vascular disorders	Hypertension	5 (6.8)	11(11.1)	4 (4.0)	4 (13.3)
	Hypotension	1 (1.4)	1 (1.0)	1 (1.0)	2 (6.7)
Renal and urinary disorders	Renal failure chronic	5 (6.8)	9 (9.1)	7 (6.9)	7 (23.3)
Nervous system disorders	Headache	3 (4.1)	2 (2.0)	1 (1.0)	2 (6.7)
Blood and lymphatic system disorders	Anemia	2 (2.7)	2 (2.0)	5 (5.0)	2 (6.7)

(Reviewer's table)

In both the pooled and non-pooled studies, there was no apparent increase in the incidence of AEs with higher RLY 5016 starting dose, mean dose and total dose.

7.5.2 Time Dependency for Adverse Events

The duration of exposure to RLY5016 varied widely across the pooled studies, ranging from 4 weeks in Study 202 to 52 weeks in Study 205 (subjects in Studies 204 and 301 were treated for 8 and up to 12 weeks, respectively). Most adverse events that occurred were observed within the first 4 weeks of treatment. The frequency of certain chronic conditions reported as adverse events including hypertension and chronic renal failure were initially reported somewhat later (within 8 weeks). There was a slight increase over time in the percentage of subjects treated with RLY5016 who had one or more AEs, which is consistent with the increase expected with longer duration of follow up.

Table 45: Common Adverse Events Occurring in ≥ 2% of Subjects Treated with RLY5016 Overall by Time Period (Safety Population)

Adverse events		RLY5016 FOS N = 666		
		Through Week 4	Through Week 8	Through Week 12
Subjects with at least One Adverse Event		222(33.3%)	284(42.6%)	306(45.9%)
Gastrointestinal Disorders	Constipation	38 (5.7%)	43 (6.5%)	46 (6.9%)
	Diarrhea	19 (2.9%)	23 (3.5%)	24 (3.6%)
	Flatulence	12 (1.8%)	13 (2.0%)	13 (2.0%)
	Nausea	11 (1.7%)	12 (1.8%)	12 (1.8%)
	Abdominal discomfort	7 (1.1%)	8 (1.2%)	9 (1.4%)
Metabolism and nutrition disorders	Hypomagnesaemia	12 (1.8%)	17 (2.6%)	19 (2.9%)
	Hyperglycemia	6 (0.9%)	10 (1.5%)	11 (1.7%)
	Hypoglycemia	3 (0.5%)	5 (0.8%)	5 (0.8%)
Vascular disorders	Hypertension	9 (1.4%)	17 (2.6%)	18 (2.7%)
Renal and urinary disorders	Renal failure chronic	8 (1.2%)	14 (2.1%)	17 (2.6%)
Nervous system disorders	Headache	7 (1.1%)	8 (1.2%)	10 (1.5%)
Cardiac disorders	Supraventricular extrasystoles	7 (1.1%)	11 (1.7%)	12 (1.8%)
	Ventricular extrasystoles	6 (0.9%)	7 (1.1%)	9 (1.4%)
Blood and lymphatic system disorders	Anemia	6 (0.9%)	10 (1.5%)	11 (1.7%)
General disorders	Peripheral edema	6 (0.9%)	8 (1.2%)	9 (1.4%)

(Reviewer's table)

In Study 205, in which subjects were treated for up to a year, the incidence of constipation decreased over time. The incidence of some TEAEs including hypomagnesaemia, urinary tract infection, hypertension, and chronic renal failure tended to be greater in this study possibly reflecting the longer follow-up times (data not shown here).

7.5.3 Drug-Demographic Interactions

To evaluate the possible effect of demographic factors on the safety of RLY5016, subgroup analyses were performed in the pooled studies by gender, age, and region. In general, there was no suggestion of a drug-demographic interaction. These data are discussed briefly below:

- *AEs by gender:* In the pooled studies, 400 of the 666 subjects in the RLY5016 for Oral Suspension group were men and 266 subjects were women. Of the 20 subjects who died, 17 were male and 3 were female. All of these deaths were considered to be related to the primary diseases. In general, there were no gender differences in RLY5016 related TEAEs.
- *AEs by age:* In the pooled studies, 268 of the 666 subjects (40.2%) in the RLY5016 group were < 65 years of age, and 398 subjects (59.8%) were ≥ 65 years of age. Overall, subjects age 65 and older reported more gastrointestinal and cardiovascular events including constipation (9.5% vs. 3.7%), diarrhea (6.0% vs. 3.0%), cardiac arrhythmias

(11.1% vs. 8.2%) and cardiac failure (2.3% vs. 1.4%) than younger patients. However, interpretation of these analyses is confounded by potential differences in coexisting comorbidities and/or severity of comorbidities that are associated with older age in the population.

- *AEs by region*: In the pooled studies, 456 of 666 subjects (68.5%) in the RLY5016 group were from non-EU countries (i.e., Georgia, Russia, Serbia and Ukraine) and 210 subjects (31.5%) were from the US and EU countries (i.e., Czech Republic, Croatia, Denmark, Hungary, Germany, Italy, Poland, and Slovenia). Of the 20 subjects who died, 15 were from sites in non-EU countries, 5 were from sites in EU countries, and none were from sites in the US. This difference likely reflects the higher number of subjects from non-EU countries participating in the clinical studies. In subjects treated with RLY5016, subjects in the non-EU geographic region, compared with the US and EU geographic region, had a lower overall incidence of AEs including renal events (6.4% vs 11.0%), cardiovascular events (10.1% vs 14.3%), gastrointestinal events (11.8% vs 37.6%), hypomagnesaemia (4.8% vs 6.2%) and hypokalemia (0.7% vs 3.3%). The reasons for these differences in the overall rates of AEs reported by geographic region are not clear. Given that RLY5016 is an oral, non-absorbed drug, it is unlikely that the observed differences for some of these AEs reflect true differences in the safety profile of this drug. In contrast, some adverse events, such as GI events, could be caused by the drug. The difference in GI events between the non-EU countries and EU/ US countries include constipation (3.3% vs 15.7%); diarrhea (2.6% vs 9.5%); flatulence (0.7% vs 4.8%); nausea (1.1% vs 4.8%); and vomiting (0.9% vs 3.8%). Site inspections were conducted in non-EU countries; no issues related to data integrity were identified based on the Office of Science Investigation report.

7.5.4 Drug-Disease Interactions

Adverse events were analyzed in patients with different primary diseases including diabetes, CKD, heart failure, myocardial infarction and hypertension. There were no clear drug-disease interactions.

7.5.5 Drug-Drug Interactions

An *in vitro* test system was used to evaluate potential interactions between RLY5016 and a set of 28 orally-administered compounds commonly used in the target patient population. The set of compounds tested included prototypical drugs from many classes likely to be administered in patients receiving RLY5016 including antihypertensives, anticoagulants, lipid modifying agents, antihyperglycemics, cardiac medications, antibiotics, and oral hormones (levothyroxine). No formal human drug interaction studies were performed with RLY5016. The results of *in vitro* interaction studies are discussed in Sections 7.2.3 and 4.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the pooled studies of up to one year duration, one case of colon cancer was reported. No other malignant tumor was reported.

7.6.2 Human Reproduction and Pregnancy Data

There is no information on drug exposure in pregnant or lactating woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: There were no accidental or intentional overdoses of RLY5016 in the clinical studies. A total of 9 subjects in the pooled clinical studies had large dose increases, defined as increases of ≥ 3 times the magnitude of the previous dose of RLY5016. All of these increases occurred within the first week of study treatment (Day 3 to Day 8), and all were the result of protocol-specified increases in RLY5016 dose because of elevated serum potassium values. For 5 of the 9 subjects with large dose increases, no AEs were reported. The remaining 4 subjects with large dose increases had non-serious AEs recorded within 14 days of the increase. These adverse events, which included hypokalemia, hypomagnesaemia, diarrhea and hypertensive crisis, are described below.

- One subject had an increase in dose of RLY5016 from 8.4 g/day to 25.2 g/day patiromer on Day 3. On Day 12, the subject had AEs of moderate hypokalemia and moderate hypomagnesaemia. The dose of RLY5016 was not changed because of the events. The hypokalemia and hypomagnesaemia events resolved on Day 22 and Day 29, respectively. The subject completed the study.
- One subject had an increase in dose of RLY5016 from 16.8 g/day to 50.4 g/day patiromer on Day 3. On the same day, the subject had an event of moderate diarrhea that resulted in withdrawal of RLY5016. The subject withdrew consent for participation in the study. The last study visit was on Day 4. The event resolved on Day 5.
- One subject had an increase in dose of RLY5016 from 16.8 g/day to 50.4 g/day patiromer on Day 8. On Day 12, the subject had a moderate hypertensive crisis. The dose of RLY5016 was not changed. The subject was treated with medication and the event resolved on the day of onset.
- One subject had an increase in dose of RLY5016 from 8.4 g/day to 50.4 g/day patiromer on Day 3. On Day 4, the subject had mild diarrhea. The dose of RLY5016 was not changed because of the event. The event resolved on Day 8.

Abuse potential and withdrawal symptoms: Not applicable given the drug's mechanism of action/therapeutic class.

7.7 Additional Submissions / Safety Issues

None

8 Post market Experience

There is no postmarketing experience with this product.

9 Appendices

9.1 Literature Review/References

I searched Pubmed using the key words: potassium binders, hyper-/hypokalemia, or hypomagnesaemia. Rare cases of GI necrosis and perforation and complications of sodium overload have been reported with sodium polystyrene sulfonate. No additional safety concerns associated with potassium binders were identified beyond those discussed elsewhere in this review.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held.

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/s/

SHEN XIAO
06/19/2015

ALIZA M THOMPSON
06/19/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205-739 **Applicant:** Relypsa, Inc. **Stamp Date:** October 21, 2014

Drug Name: Veltassa (patiromer) **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: *RLY5016-205* Study Title: *A multicenter, randomized, open-label, dose ranging study to evaluate the efficacy and safety of RLY5016 in the treatment of hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without Spironolactone.* Sample Size: *306 subject* Arms: *3* Location in submission: *M 5.3.5*	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study : *RLY5016-301,"A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of*	x			At the EOP2 meeting, the Agency stated that RLY5016-301, as designed (with a

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Patiromer for the Treatment of Hyperkalemia Indication: *Hyperkalemia*				randomized withdrawal phase), could be considered two distinct trials, both of which could be used to support approval.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	The product is not substantially absorbed. At the EOP2 meeting, the sponsor was told that a Thorough QT study would not be needed.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				The number of patients exposed does not meet the numbers referenced in the footnote. The proposed indication is for the treatment of hyperkalemia. What the label will say (b) (4) will be determined during the review.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Shen Xiao — *see electronic signature*
Reviewing Medical Officer — Date

Aliza Thompson — *see electronic signature*
Clinical Team Leader — Date

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

/s/

SHEN XIAO
12/03/2014

ALIZA M THOMPSON
12/03/2014