



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Veltassa

Common name: patiomer

Procedure No. EMEA/H/C/004180/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ADME	absorption, distribution, metabolism and elimination
AE	adverse events
ARB	angiotensin II receptor blocker
AUC	area under the curve
BB	beta blockers
BID	twice per day
BMI	body mass index
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
DBP	diastolic blood pressure
EU	European Union
ERA	environmental risk assessment
FDA	US Food and Drug Administration
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GCP	Good Clinical Practice
HED	human equivalent dose
HF	heart failure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ITT	intent-to-treat
IU	International Units
LS	least squares
MRHD	maximum recommended human dose
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PVA	Polyvinyl alcohol
QD	once per day
QTPP	Quality target product profile
RAASi	renin angiotensin aldosterone system inhibitor
RH	Relative Humidity
RLY5016	patiromer calcium salt
RLY5016H	patiromer anion
RLY5016S	patiromer sorbitex calcium
RMP	risk management plan
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
T2DM	type 2 diabetes mellitus
TID	three times per day
TIP	treatment initiation period

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vifor Fresenius Medical Care Renal Pharma France submitted on 15 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Veltassa, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 February 2015.

The applicant applied for the following indication: Treatment of hyperkalaemia in adult patients

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that patiromer sorbitex calcium was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0235/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0235/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance patiromer sorbitex calcium contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: David Lyons

- The application was received by the EMA on 15 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 August 2016.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 April 2017.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 25 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 May 2017.
- During the CHMP meeting on 15-18 May 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 15-18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Veltassa on 18 May 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Elevation of the plasma potassium concentration decreases the ratio of intracellular to extracellular potassium, leading to partial depolarization of the cell membrane. These physiological effects of hyperkalaemia can result in muscle weakness, paralysis, life-threatening effects on cardiac conduction (e.g., QRS widening), arrhythmias such as ventricular fibrillation and sudden death. Thus, hyperkalaemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with increased mortality risk. While rare in the healthy individuals with normal renal function, the prevalence of hyperkalaemia in patients with renal insufficiency or chronic kidney disease (CKD) ranges from 5% to 50% and increases as renal function declines. Thus, patients most at risk of hyperkalaemia are those with compromised renal excretion of potassium, primarily patients with CKD and/or patients being treated with drugs that inhibit renal potassium excretion, including renin angiotensin aldosterone system inhibitors (RAASi). RAASi are used in the treatment of hypertension, CKD and congestive heart failure and compelling data and clinical practice guidelines support the use of RAASi to reduce adverse cardiovascular and renal outcomes in certain high-risk patient populations. However, therapy with RAASi can be limited by hyperkalaemia resulting from treatment with these medications. In addition to CKD and the use of RAASi, diabetes and the use of beta-blockers can increase the risk of hyperkalaemia leading to fatal cardiac arrhythmias.

2.1.2. Epidemiology

Based upon 2015 population estimates of 508 million persons in the European Union (EU) and 320 million in the US, it is estimated that 3.8 million patients will present with hyperkalaemia each year in the EU and approximately 2.4 million patients in the US.

2.1.3. Clinical presentation, diagnosis

Potassium balance is regulated in part by secretion of potassium into the colon through a passive paracellular route and active secretion. Hence in the colon, potassium is at high concentration relative to other cations. In CKD, urinary excretion of potassium decreases and colonic secretion of potassium increases substantially. Hyperkalaemia can present as a consequence of a number of acute clinical conditions that occur in a hospital setting. Based on literature data, approximately 14% of patients experienced a hyperkalaemic event and the rate was higher in patients with CKD than in those without CKD. Acute clinical conditions such as tumour lysis syndrome, rhabdomyolysis, crush injuries, massive blood transfusions and acute renal failure can each lead to a rise in serum potassium to high levels. These acute clinical conditions require immediate treatment for the hyperkalaemia, particularly when the degree of hyperkalaemia is severe (e.g., serum potassium ≥ 6.5 mEq/L) and/or associated with cardiac repolarization disturbances. The risk of death is increased significantly in CKD patients with hyperkalaemia, underscoring the need to treat this clinical condition.

2.1.4. Management

The approach to managing patients with acute hyperkalaemia due to reversible underlying conditions differs somewhat from the approach to managing patients whose underlying conditions contributing to hyperkalaemia are more persistent and chronic in nature. Patients with severe acute hyperkalaemia, or with electrocardiogram (ECG) changes related to hyperkalaemia, are generally already hospitalized or sent to the hospital for treatment. The therapeutic goals in such hospitalized patients with severe hyperkalaemia are: temporarily stabilisation of the myocardium, temporarily shift in intracellular potassium and utilisation of treatments that remove potassium from the body, which are intended to reduce the risk for developing a fatal cardiac arrhythmic event. For patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of RAASi therapies, the traditional approach to management has relied on dietary potassium restriction, RAASi dose reduction or discontinuation, diuretics, oral bicarbonate and if applicable, the use of the cation exchange resins sodium polystyrene sulfonate or calcium polystyrene sulfonate. The use of dietary potassium restriction to manage hyperkalaemia is difficult due to the ubiquitous presence of potassium in foods.

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are two cation-exchange resins currently approved in the EU for the treatment of hyperkalaemia. They were introduced in the 1950s and 1960s; however, have not been rigorously studied. There are limited prospective, long-term clinical trial data available to understand the safety and efficacy of these agents. These products are not well tolerated and their use can be associated with life-threatening side effects including intestinal necrosis. Further, an appreciable sodium load can occur with sodium polystyrene sulfonate such that caution is advised when sodium polystyrene sulfonate is administered to patients who cannot tolerate even a small increase in sodium loads. These issues make the administration of sodium polystyrene sulfonate for prolonged durations of time difficult. Additionally, calcium and sodium polystyrene sulfonate are contraindicated for treating patients with a serum potassium < 5.0 mEq/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing. Thus, there is a need for new therapeutics for hyperkalaemia whose efficacy and safety are well characterized and can be administered long term.

About the product

Veltassa, powder for oral suspension, contains a new chemical entity (RLY5016S) belonging to the pharmacologic class of potassium binders. The active moiety, patiomer, is a non-absorbed, cation-exchange polymer that binds potassium predominantly in the lumen of the colon where potassium is the most abundant cation. This increases faecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in hyperkalaemic patients.

The applied for indication of Veltassa is treatment of hyperkalaemia in adult patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for oral suspension containing 8.4 g, 16.8 g or 25.2 g of patiomer (as patiomer sorbitex calcium) as active substance.

The other ingredient of the product is xanthan gum.

Veltassa is a non-absorbed cation exchange polymer manufactured as free-flowing spherical beads of approximately 100 micrometer diameter which are taken orally. The beads are of a size that is not

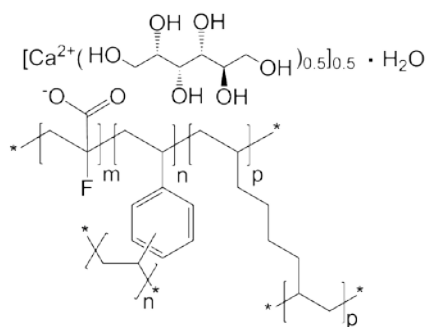
absorbed. It increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen resulting in a reduction of serum potassium levels.

The product is available in sachets made of five layers: polyethylene, aluminium, polyethylene, polyester and paper as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The active substance, patiromer sorbitex calcium (RLY5016S), is a crosslinked polymer anion of patiromer (RLY5016H) with calcium-sorbitol counterion. The chemical name of patiromer sorbitex calcium is poly[(*D*-glucitol-calcium) 2-fluoroacrylate-co-diethenylbenzene-co-octa-1,7-diene] corresponding to the molecular formula $(\text{Ca}_2\text{C}_6\text{H}_{14}\text{O}_6)_m(\text{C}_3\text{H}_2\text{FO}_2)_{4m}(\text{C}_{10}\text{H}_{10})_{4n}(\text{C}_8\text{H}_{14})_{4p}$. The active substance contains approximately 15% water. The structure of patiromer sorbitex calcium is shown in Figure 1. No regular order of the monomers is implied by the structure; crosslinking is expected to occur randomly along the polymer chains.



m = number of 2-fluoro-2-propenoate groups $m = 0.91$
 n, p = number of crosslinking groups $n + p = 0.09$
 * H_2O = associated water
 * = indicates an extended polymeric network

Figure 1. Structure of patiromer sorbitex calcium.

The chemical structure of the patiromer sorbitex calcium comprises three repeating units: a negatively charged 2-fluoro-2-propenoate and two difunctional molecules (divinylbenzene and 1,7-octadiene) that crosslink the polymer. As mentioned above, calcium-sorbitol complex is the counter-ion to the negatively charged and cross-linked polymer anion.

The structure of the active substance was investigated using FTIR spectroscopy, solid-state ^{13}C nuclear magnetic resonance (^{13}C -NMR) spectroscopy, elemental analysis for fluorine by oxygen combustion and ion selective electrode (ISE), elemental analysis for calcium by ion chromatography (IC), analysis of sorbitol content by liquid chromatography with refractive index detection (LC-RI), determination of water content from loss on drying by gravimetry, and patiromer anion content by calculation. The calcium-sorbitol complex, which is the counterion to the negatively charged polymer anion, was characterised by ^{43}Ca -NMR spectroscopy. In addition, the equilibrium binding of sorbitol to the patiromer calcium salt form of the polymer (RLY5016), and a comparison of the stabilizing effect of sorbitol were provided as evidence of the calcium-sorbitol counterion complex.

Patiromer sorbitex calcium is an amorphous, free flowing yellow-brown non-hygroscopic powder composed of individual spherical beads. Each crosslinked polymer bead represents one macromolecule that has multiple covalent crosslinks between polymer chains. The weight of a bead is dependent on its size and patiromer sorbitex calcium exhibits a distribution in particle size, which is controlled in the active substance specification (see specifications section). The molecular weight for a 100 micrometer bead was estimated to be 5.6×10^{17} g/mol.

The active substance is insoluble in water, 0.1 M HCl, methanol and n-heptane.

Manufacture, characterisation and process controls

The applicant has described the manufacture of the active substance, along with its control of materials, critical steps, in-process control and process validation.

Patiromer sorbitex calcium is manufactured in two main steps (suspension polymerization and post polymerisation processing) using commercially available well defined starting materials with acceptable specifications .

During the evaluation there was a major objection regarding the potential absorption and accumulation of the polymer beads. It was clarified that in order to overcome the risk of absorption of small particles and ensure these are not formed, the active substance manufacturing process was designed to manufacture polymer beads with an adequate diameter and a narrow particle size distribution. The main steps to achieve this objective and to avoid the formation of particles smaller than 1 µm, which may be absorbed, were adequately described.

The absence of small particles is ensured by the manufacturing process. In addition, the respective particle size distribution is controlled by tight specifications.

To demonstrate that the RLY5016 polymer is not systemically absorbed after oral administration and is excreted in the faeces, two single-dose absorption, distribution, metabolism and elimination (ADME) studies with radiolabelled RLY5016 were performed in rats and dogs. Plasma, faecal and urinary monitoring from both studies demonstrated the non-absorbed nature of the polymer and its lack of systemic bioavailability.

Process control for the manufacture of patiromer sorbitex calcium is achieved through specifications of the input materials and intermediates, in-process controls (IPCs) and established process hold points. There was an extensive investigation of process parameters and associated ranges to ensure a robust process that produces active substance which consistently meets the quality criteria.

The applicant has provided a large amount of manufacturing development data including a discussion of quality target product profile, quality risk assessments to establish critical quality attributes and critical process parameters as determined using design of experiments and edge of failure experiments. The manufacturer has then outlined ranges of process parameters which are proven acceptable ranges (PARs). No design space has been defined. The available development data, the proposed control strategy and batch analysis data fully support the proposed PARs.

The critical quality attributes for patiromer sorbitex calcium are: calcium content, patiromer anion content, sorbitol content, total potassium exchange capacity, particle size distribution, loss on drying, impurities and fluoride. The critical process parameters have been adequately described.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. In addition, carryover, spiking and depletion studies have been carried out on impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The differences between the different manufacturing process used during development and the process registered for each manufacturing site have been adequately explained. The manufacturing process development for RLY5016S was carried out in three development stages:

The first stage was the early development stage where the RLY5016 polymeric structure was developed with the desired potassium binding characteristics. At this stage of development, RLY5016, the calcium salt form of the polymer, was produced as the active substance.

In the second stage of development, sorbitol was introduced into the polymer to yield the calcium-sorbitol counterion, resulting in a more stable form of the drug substance, RLY5016S, by minimizing degradation.

In the third stage of development, the commercial process with enhanced control strategies and improved process robustness was developed.

A comparability assessment to evaluate the equivalence of active substance manufactured by the different manufacturing sites was conducted. The assessment involved comparison of manufacturing processes, batch analysis data, impurity profiles, physicochemical characterization, and stability trends. The comparison of process elements resulted in the conclusion that the minor differences between the processes used at the different sites had no impact on the active substance quality.

The active substance is packaged in a low density polyethylene (LDPE) bag, which in turn is placed into a second outer LDPE bag. The sealed, double-bagged active substance is enclosed in a drum. The LDPE bags used as the primary container meet the requirements set forth in the Ph.Eur. monograph 3.1.3. Polyolefines and the EU Directive 10/2011 and its amendments for plastics with food contact. The differences in container closure system between sites are not considered significant and their use is justified by stability data.

Specification

The active substance specification includes tests for appearance, identity (FTIR, fluorine content by oxygen combustion/F-ISE, calcium by IC), calcium content (IC), patiromer anion content (calculation), sorbitol content (LC-RI), total potassium exchange capacity (IC), rate of potassium exchange (IC), particle size distribution (laser diffraction), loss on drying (gravimetry), swelling index (gravimetry), residual solvents (HS-GC-FID), unspecified impurities (HS-GC-FID), related substances (SEC-RI), process impurities (IC), elemental impurities (ICP-MS), fluoride (F-ISE), microbial enumeration tests (Ph. Eur) and specified microorganisms (Ph. Eur).

Methods have been satisfactorily validated.

Adequate toxicological data have been provided to support the proposed limits for relevant impurities. Elemental impurities are controlled in accordance with the recommendations of ICH Q3D guideline. . Limits were based on batch analysis and are well within limits established toxicologically.

The microbiological testing limits are based on Ph. Eur. 5.1.4 requirements for non-sterile dosage forms and are accepted.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards has been presented.

Batch analysis data on up to 30 pilot and up to 7 commercial scale batches of the active substance from the proposed manufacturing sites are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale stability batches of active substance manufactured at each of the proposed manufacturing sites, packaged in a container closure system representative of that intended for the market and stored for 36 months under long term conditions at 2-8 °C and for up to 6 months under accelerated conditions at 25 °C / 60% RH according to the ICH guidelines were provided.

The following parameters were tested on the pilot scale batches: appearance, total % calcium, patiromer anion content, sorbitol content, potassium binding capacity, particle size distribution, loss on drying, residual starting materials, residual solvents, extractable impurities, total unspecified impurities, fluoride, swelling, total potassium exchange capacity (TKEC), total aerobic microbial counts, total combined yeast and molds *Salmonella*, *Escherichia coli* *Staphilococcus aureus* and *Pseudomonas aeruginosa*.

Additional stability data from the first three commercial scale batches from each manufacturer stored at long term (2-8 °C) conditions for up to 9 months and accelerated conditions for 6 months were provided.

The following parameters were tested on the commercial scale batches: appearance, loss on drying, extractable polymeric impurities, largest single unspecified impurity, total unspecified impurities, fluoride, total potassium exchange capacity, total aerobic microbial counts, total combined yeast and molds and E.coli. The analytical methods used were the same as for release and were stability indicating.

All parameters remained constant or within the analytical method variability over the duration of the stability study and met the acceptance criteria with the exception of fluoride, which exceeded the acceptance criteria after storage under accelerated conditions.

A forced degradation study and a photostability study (per ICH Q1B) were conducted on three pilot scale batches. Samples were exposed to acid, base, thermal, and oxidative stress. Samples exposed to all the stress conditions were analyzed for sorbitol content, total potassium exchange capacity, fluoride content, methanol, individual unspecified impurities and extractable polymeric impurities. Appearance was tested after exposure of the active substance to the thermal stress condition only.

The results of the forced degradation study demonstrated that exposure to acid, base, oxidative and thermal stress did not significantly impact the parameters tested except of fluoride. Fluoride was the only degradant obtained in significant amounts, as expected, upon exposure of the active substance to thermal stress conditions. However, the exposure to acid, base and oxidative stress resulted in minimal change in fluoride.

The photostability testing demonstrated that the active substance shows some photosensitivity upon exposure to ICH Q1B, Section 1B Option 2 conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product, Veltassa, is a powder for oral suspension intended to be administered orally after suspending in water, apple juice or cranberry juice. The product is available in single dose sachets made from five layer (Paper/Polyester/PE/Aluminium Foil/PE) laminate web stock that is heat sealed on four sides.

The active substance is designed to bind potassium in the lumen of the colon. The product is available in three strengths containing 8.4 g, 16.8 g and 25.2 g of patiromer (as patiromer sorbitex calcium).

As indicated above, the active substance, patiromer sorbitex calcium, is an amorphous, free-flowing powder that is composed of individual spherical beads. The particle size distribution of the active substance is controlled to ensure consistent product manufacturability and finished product with the desired quality attributes. It was confirmed that the particle size is large enough to prevent absorption via transcellular or paracellular routes through intestinal epithelial cells.

The quality target product profile (QTPP) was to develop a safe and efficacious powder for suspension formulation that required a minimum quantity of diluent for suspension. The formulation was designed to contain a minimal number and amount of excipients to keep the total amount of powder per dose and volume of diluent necessary for suspension of the polymer as low as possible. A suspending agent is the only excipient included in the formulation.

Throughout development different formulations were used in clinical studies. The commercial formulation is composed of patiromer sorbitex calcium and xanthan gum, used as suspending agent which ensures that the finished product remains suspended upon the addition of water or juices (when prepared as directed). Xanthan gum is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

To prove the suitability of potential excipients for the preparation of dosage forms, excipient compatibility studies were performed on binary mixtures of active substance and excipients. No relevant interaction between any excipient and the active substance was observed. These results support the acceptability of all the excipients used during clinical studies and the intended commercial formulation.

The formulations evaluated during development provide a suspension upon mixing with a small amount of water.

In this regard, a suspendability and pourability experiment was conducted to determine the quantity of water for suspension of the finished product. The results from these studies demonstrate that all dosage strengths can be suspended in 80 ml of water, apple or cranberry juice to yield a suspension that can be administered. The preparation instructions are described in section 4.2 of the SmPC.

Studies were conducted to demonstrate that the finished product is compatible with water, apple juice or cranberry juice. The studies demonstrated that the finished product can be suspended in water, apple juice or cranberry juice without adversely impacting the quality of the suspension achieved or the binding capacity and stability of patiromer.

As mentioned above, patiromer sorbitex calcium is a cross-linked polymer that does not require systemic absorption for its therapeutic or pharmacologic effect. The polymer remains intact in the gastrointestinal tract where it exerts its potassium binding effect.

The total activity of Veltassa is determined by *in vitro* potassium exchange. The total potassium exchange capacity (TKEC) assay measures the total binding sites of the active substance in the finished product. This test is performed as a finished product batch release and stability test.

The primary packaging consists of sachets made of five layers: polyethylene, aluminium, polyethylene, polyester and paper. The sachet is opaque, provides protection against light and ingress of water and is compatible with the drug product. The product contact surface (polyethylene layer) of the sachet is suitable for food contact. The manufacturer of the sachet has declared that all constituents are listed in Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food and all its amendments. He has also declared that the polyethylene layer (the product contact surface) meets the requirements of European Pharmacopoeia 3.1.3 "Polyolefins" materials used for the manufacture of containers and the requirements of European Pharmacopoeia 3.1.4 "Polyethylene without

additives for Containers for Parenteral Preparations and for Ophthalmic Preparations". The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: pre-blend preparation, dry blending and filling/packaging. The process is considered to be a standard manufacturing process.

As described above, Veltassa is available in three strengths and two different packaging configurations.

Process validation activities for the finished product manufacturing process were performed at the commercial manufacturing site. Satisfactory process validation data on three batches of each strength were provided.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, suspendability, identification (FTIR, presence of calcium), patiromer anion content (gravimetry), uniformity of dosage units (Ph. Eur.), total potassium exchange capacity (IC), calcium content (IC), loss on drying (gravimetry), fluoride (F-ISE), extractable impurities (HPLC-UV), total aerobic microbial count (Ph. Eur.), total combined yeasts and molds count (Ph. Eur.) and *E. coli* (Ph. Eur.).

The product specifications cover appropriate parameters for this dosage form. It is generally compliant with ICH Q6 and the Ph.Eur. monograph on oral powders and considers appearance, identity, reconstitution and uniformity of mass.

The fluoride limit during shelf-life is in line with European Safety Authority (EFSA) recommendations for individuals aged 15 years and older (the product is not indicated below 18 years).

The limit for extractable impurities is in line with the ICHQ3B limits for impurities in new drug products, for a daily dose of greater than 2g. Microbiological limits are in accordance with the Ph.Eur.

The absence of a test for particle size, elemental impurities, residual solvents, potassium binding capacity and dissolution was justified.

The finished product is formulated as a powder for oral suspension with a site of action in the gastrointestinal (GI) tract. Veltassa is not absorbed from the GI tract. The polymer backbone remains intact in the GI tract where it exerts its potassium binding effect.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for three pilot scale batches of each strength and two commercial scale batches manufactured by the proposed finished product manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch analysis data on finished product batches produced at development sites that were used in clinical studies were also submitted.

Stability of the product

Stability data of twenty four pilot scale batches of finished product of four strengths (4.2, 12.6, 16.8 and 25.2 mg) under long term conditions for 36 months at 2-8°C and for up to 6 months under accelerated conditions at 25 °C / 60% RH according to the ICH guidelines were provided. The batches of Veltassa are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The batches were manufactured with active substance from the proposed active substance manufacturers.

Samples were tested for appearance, total % calcium, patiromer anion content, potassium binding capacity, total potassium exchange capacity, loss on drying, fluoride, extractable polymeric impurities-individual unspecified, extractable polymeric impurities-total unspecified, total aerobic microbial counts, total combined yeast and molds, *E.coli*, sedimentation and suspendability of drug product. The analytical methods used were the same as for release and were stability indicating.

All results remained within the specification limits and showed no discernible trends. The only attribute that showed an increase over time was fluoride content, but fluoride results for all batches at both storage conditions remained within the proposed acceptance criteria.

Although an out of specification result total potassium exchange capacity was observed , it was considered to be sampling related, and the issue was addressed in later timepoints. Also one of the twelve lots did not meet the proposed acceptance criteria for patiromer anion at release, however they all meet the stability acceptance criterion.

An in-use stability study was also conducted on eight pilot scale batches of Veltassa. The purpose of this study was to justify in-use storage at 25°C after long term storage at 2-8°C. The stability of drug product was monitored to ensure specifications are maintained for specified time points at 25°C/60% RH after long-term storage at 2 – 8°C.

Appearance, total % calcium, patiromer anion content, potassium binding capacity, total potassium exchange capacity, loss on drying, extractable impurities, and sedimentation showed no discernible trend. Suspendability of drug product was added as a stability attribute at the 24-month stability time point and tested for all lots. As expected, the only stability attribute that showed an increase during the in-use period was fluoride, but fluoride levels were still within the stability protocol specification. . Therefore, the registration in-use studies demonstrated that RLY5016 Powder for Oral Suspension can withstand storage at 25°C/60%RH for at least 6 months following storage at 2 – 8°C for up to 30 months. This study demonstrated that the finished product can be stored for up to six months at room temperature after removal from the refrigerated storage condition. This in-use period will be within the total approved shelf-life of 36 months.

A controlled room temperature feasibility study was also conducted, whereby one batch was evaluated at 2-8°C, 25°C/60%RH, 30°C/65%RH and 40°C/75%RH, in order to support limited in-use room temperature storage and to evaluate the impact of excursions on drug product stability. The usual specification, with minor differences being inclusion of microbial quality testing, and using sedimentation rather than suspendability were applied. No discernible trend was noted for appearance, total % calcium, patiromer anion content, potassium binding capacity, total potassium exchange capacity, loss on drying, extractable impurities, and sedimentation. All results met the stability protocol acceptance criteria and the commercial acceptance criteria. As expected however, a significant increase in the fluoride levels was seen at elevated temperatures Patiromer anion content stayed within both the proposed release acceptance criterion and within the proposed shelf life acceptance criterion. No evidence of microbial growth was observed.

A forced degradation study was also conducted on one batch. Samples were exposed to heat, H₂O₂, acid, and light. The results obtained demonstrated that the finished product was relatively stable to most of the stress conditions applied. The fluoride ion was the only degradant obtained on exposing the product to base, heat or light stress. The total potassium exchange capacity was unaffected by exposing the finished product to acid, base, heat, oxidative and light. Similarly exposure to light did not affect the appearance of the product, the patiomer content, extractable impurities, potassium binding capacity or the total potassium exchange capacity. A small but noticeable increase in the fluoride levels was obtained when the finished product was exposed to light. The stability-indicating nature of the analytical procedures was adequately demonstrated.

Based on available stability data, the proposed shelf-life of 36 months at 2°C – 8°C, with an in-use period allowed whereby the user may store the product at 25°C for a period of six months, within the 36 month expiry date period (i.e. 30 months 2-8°C +6 months 25°C) as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Veltassa is a powder for oral suspension containing patiomer sorbitex calcium as active substance. The active moiety, patiomer, is a non-absorbed, cation-exchange polymer that binds potassium predominantly in the lumen of the colon. This increases faecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in hyperkalaemic patients.

The two major issues with respect to (a) ensuring small particles that could be absorbed are not present in the product and (b) controlling product performance with respect to rate of potassium binding, and other concerns raised during the evaluation have been satisfactorily addressed.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

Veltassa is a powder for oral suspension, designed to treat hyperkalaemia. The proposed indication for Veltassa is for treatment of hyperkalaemia. The non-clinical development programme for RLY5016 consisted of a range of primary pharmacology, safety pharmacology, pharmacokinetic (PK) and toxicology studies, in which RLY5016 was given orally and is the same route of administration used clinically. Pharmacology studies were performed to demonstrate the ability of the polymer anion to bind to potassium in the lumen of the colon and to increase potassium faecal excretion using both in vitro and in vivo studies. The safety pharmacology studies were conducted in accordance with current Good Laboratory Practice (GLP) regulations at contract laboratories. Additionally, the PK absorption, distribution, metabolism and excretion (ADME) studies in rats and dogs were conducted in accordance with GLP. Except for an exploratory embryo-fetal development study conducted in rabbits, all studies in the toxicology program, including the definitive embryo-fetal development study in rabbits, were conducted at various independent GLP-compliant contract laboratories. The GLP status of the individual PK and toxicology studies has been provided by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacology of RLY5016 has been examined using in vitro and in vivo studies to determine the extent RLY5016 binds to potassium and increases its excretion from the GI tract. In the first of two in vitro studies, it was shown that RLY5016 is effective in ion exchange in acidic conditions similar to that encountered in the GI tract. In the second study RLY5016 was shown to bind effectively to potassium in physiological pH conditions, and that this binding was unaffected by starting acidic form.

Three animal models were used to explore the in vivo pharmacodynamic effects of RLY5016 binding to potassium. Rats and pigs with normal renal function have been used, as have rats with chronic renal failure. In each both rats and pigs following treatment with RLY5016 there was increased faecal excretion of potassium. In a rat model of hyperkalaemia in rats treated with RLY5016 there was also an increase in potassium excretion, which was reflected in a decrease in serum potassium levels.

In the context of this application, the results of the primary pharmacology fully support the proposed therapy for RLY5016 as a treatment for hyperkalaemia.

Secondary pharmacodynamic studies

Due to a lack of systemic absorption of RLY5016, no secondary pharmacodynamic studies have been performed. This is acceptable to the CHMP.

Safety pharmacology programme

The applicant has completed a battery of in vivo GLP safety pharmacology studies in rats and dogs, providing an examination of cardiac parameters and studies to test effect on the respiratory, central nervous and gastrointestinal systems. RLY5016 had no clinically relevant effects on general behaviour, locomotor activity, pulmonary function or cardiac function. The only changes of note were observed in

the gastrointestinal (GI) system. As RLY5016 is considered to be non-absorbed, its main site of action will be the GI tract.

Two GI safety pharmacology studies have been presented. Both are of identical design; however, the first study was repeated due to findings of reduced stomach emptying that were assumed to be due to the presence of residual toluene in the drug product. A similar finding was observed in the 4 week toxicology studies completed in rats and dogs. The second gastrointestinal safety study was conducted with a toluene-removed batch of RLY5016. The concern for reduced stomach emptying was not resolved by repeating the study and the inherent issue has been explained as a consequence of dose dumping to the stomach in these rat studies. There are some questionable findings with the effects with morphine as gastrointestinal transit was unaffected with this positive control; however, stomach emptying was absent in this dose group.

The CHMP considered that given that the proposed site of action for RLY5016 will be the GI tract, the concerns for reduced stomach emptying and reduced transits times observed in the rat safety pharmacology studies have not been sufficiently explored in the initial submission. Thus, the applicant was requested to discuss the implications of these findings and their potential clinical consequences. Following the submission of applicant's response and a more detailed review of the available clinical data, the CHMP concluded that this effect of reduced gastric emptying would have only limited impact in humans.

The applicant provided a detailed discussion of the potential clinical consequences of reduced stomach emptying seen in the animal safety pharmacology studies. Two techniques were utilised to measure gastric transit of RLY5016, i) charcoal marker transit, and ii) stomach weight measurement. It is argued that due to the extent of administration of RLY5016 to rats which was approximately 1.2 g, that it was inevitable that there would be reduced stomach emptying. This argument is accepted and it is agreed that charcoal marker data would suggest no decrease in the extent of gastric motility due to administration of RLY5016. An added discussion of the clinical data obtained from patients treated with RLY5016 oral suspension also supports this view, with limited serious gastrointestinal AE's associated with treatment. This is reflected in the revised RMP in the non-clinical summary table part, gastrointestinal motility as an 'Important potential risk'. 'Use in patients with severe GI disorders' is now raised as an 'Important potential risk'.

Pharmacodynamic drug interactions

No pharmacodynamic interaction studies have been conducted with Veltassa as this drug substance is not considered to be systemically absorbed. This is acceptable to the CHMP.

2.3.3. Pharmacokinetics

A number of PK studies have been completed to describe absorption, distribution, metabolism and excretion characteristics of radio labelled RLY5016 in rats and dogs. In addition, a number of in vitro studies were submitted to assess the potential of drug-drug interactions with RLY5016. A dedicated study in rats to review the effects of fluoride absorption due to degradation of RLY5016 is provided.

Absorption: Two studies have been completed in rats and dogs to examine the potential absorption of RLY5016 in vivo. Rats were dosed with up to 313 mg/kg of radiolabelled ¹⁴C-RLY5016, given as a single oral dose and blood and plasma sampling obtained pre- and post-dose for up to 72 hours. Peak levels of ¹⁴C-RLY5016 were detected in blood and plasma at 8 hours post-dose, at levels of 0.073 and 0.326 µg equivalents ¹⁴C-RLY5016 /g, respectively. This is estimated to be equivalent to 0.004% of the total dose. No further PK measurements could be taken given the low levels of ¹⁴C-RLY5016 found in the rat. Dogs

were administered a single oral dose of 350 mg/kg 14C-RLY5016, with plasma and blood sampling obtained pre- and post-dose for up to 168 hours. Peak levels of 14C-RLY5016 were obtained between 4 and 8 hours post-dose in both male and female dogs: 0.175 and 0.339 µg equivalents 14C-RLY5016/g for males, and 0.238 and 0.406 µg equivalents 14C-RLY5016/g for females. This represents equivalent exposure to 14C-RLY5016 of 0.002% of the total dose. Plasma half-life was estimated to be 127 and 98 hours in male and female dogs, respectively. The AUC measurements are extremely low, ranging from 31.6 to 51 h.µg equivalents 14C-RLY5016/g. These studies demonstrate that there is a lack of systemic bioavailability of oral RLY5016, and systemic exposure is negligible. Furthermore, the findings support the absence of toxicokinetic measurements, carcinogenicity and pre/post natal toxicity studies.

Distribution: Distribution of radiolabelled RLY5016 was measured following whole body radiography of a single oral dose of 313 mg/kg to male rats. Distribution was limited to stomach, caecum and intestine (small and large) with most administered material detected at 4 hours post-dose, and none at 72 hours post-dose. As described earlier, analysis of plasma samples obtained from the rat and dog PK study have shown that 0.004% and 0.002% of the administered radiolabel was present in plasma in the rat and dog, respectively.

Metabolism: No specific non-clinical metabolism studies have been conducted with RLY5016. As the polymer is not absorbed, the normal process of metabolism in vivo is not expected. As a result, stability studies of the polymer have been performed using faecal samples obtained from treated humans. Polymers obtained from faecal samples were physically intact, and there was no difference in cation binding capacity of GI passaged, and non-passaged RLY5016. RLY5016 has been demonstrated to be metabolically stable.

Excretion: Recovery of RLY5016 has been described in the two ADME studies, in rat and dog. Recovery of the radiolabelled RLY5016 in faeces and urine was 84% and 0.15%, respectively, in rats and 99.9% and <0.1%, respectively, in dogs. Lower recovery in rat faeces was attributed to difficulties in obtaining material and in homogenising the rat samples.

Pharmacokinetic interactions: Given the non-absorbed nature of RLY5016, pharmacokinetic drug-drug interactions are more likely to occur with other co-administered drugs in the GI lumen vicinity. This interaction may affect absorption and distribution of drugs other than RLY5016. The applicant developed a quantitative structure-property relationship (QSPR) based model to predict binding of drugs to RLY5016S using knowledge of a drug's surface area of acceptor atoms, ionisation potential and lipophilicity. In addition, an in vitro test system was used which measured free levels of 28 medicinal products concentrations after incubation in the presence or absence of RLY5016S. Three test matrices were used as representative of pH conditions in the GI tract. Of the 28 selected products, amlodipine, cinacalcet, ciprofloxacin, clopidogrel, furosemide, levothyroxine, lithium, metformin, metoprolol, trimethoprim, verapamil and warfarin were taken forward to human drug-drug interaction studies. Interactions have been identified with ciprofloxacin, levothyroxine and metformin. Hence, section 4.5 of the SmPC adequately reflects the findings of the in vitro studies in order to inform the treating physicians about the possible interactions.

No examination of interactions with drug transporters or CYP enzymes was conducted, and absence of these studies is acceptable to the CHMP.

Other PK studies: A study to evaluate fluoride absorption in a rat model has been presented. Male rats were administered sodium fluoride, calcium fluoride, sodium and calcium loaded RLY5016, and absorption of fluoride was compared. It was demonstrated that RLY5016 complexed with calcium resulted in lower systemic absorption of fluoride compared to RLY5016 complexed with sodium. Lower exposure to fluoride would therefore be expected from RLY5016, which is complexed to calcium.

2.3.4. Toxicology

Single dose toxicity

Acute toxicity was not evaluated in non-clinical species; this is due to the lack of systemic absorption of RLY5016. This approach is agreed and further characterisations of acute effects are recorded in the rat in vivo micronucleus study and rat 2 week dose range finding study. Similar dose ranging study was conducted in dogs. Predominate effects were limited to diet related changes, due to high dosage of compound in feed.

Repeat dose toxicity

Repeat dose oral toxicity studies have been performed for up to 6 months in rats and for up to 9 months in dogs. Concerns were raised in earlier studies with RLY5016 which contained residual levels of toluene which resulted in higher than expected adverse findings and as a result 4 week repeat dose studies in both rats and dogs were repeated with a toluene-free product. The 4- and 26-week studies were completed in rats and given the lack of systemic exposure of RLY5016, no target organs were identified. With the toluene-free product there was no mortality with dosing up to 13.3 g/kg/day. The most significant finding was of increased food consumption, observed in both male and female rats and noted in the 4 week and 26 week studies. The NOAEL determined from the 26 week study was >5 g/kg/day, the highest dose administered. This represents a clinical safety margin of 10 based upon a maximum recommended human dose (MRHD) of 30 g/day (0.5 g/kg/day for a 60 kg human).

In dogs, oral toxicity studies were performed for 4 and 39 weeks. There was no mortality at any dose and no target organ for toxicity was determined. Adverse findings were limited to faecal changes and slight decreases in to body weight and food consumption. In the 39-week study there were instances of atrophy of seminiferous tubules in male dogs, and inflammation of heart coronary arteries. These changes were low in number and a case for being spontaneous can be supported. The NOAEL determined from the 39 week study was 3.75 g/kg/day, the highest dose administered and this represents a clinical safety margin of 7.5 based upon a maximum recommended human dose (MRHD) of 30 g/day (0.5 g/kg/day for a 60 kg human). The HED from dog to human is 2 g/kg/day, and a safety margin of 4.

No toxicokinetic data has been supplied for any study in either species. The absence of exposure data is justified given the lack of systemic exposure of RLY5016 as determined in the non-clinical PK studies. As no toxicokinetic measurement were taken during the completion of the repeat dose toxicity studies in rats and dogs, this approach was justified due to the non-absorbed nature of RLY5016 in both species.

NOAELs were established in each species, 5 g/kg/day in rats and 3.75 g/kg/day in dogs. In rats the NOAEL of 5 g/kg/day represents a clinical safety margin of 10 based upon a maximum recommended human dose (MRHD) of 30 g/day (0.5 g/kg/day for a 60 kg human). A conversion to body surface area (BSA) was not done in order to normalise across species to gastrointestinal volume. Using BSA conversion of rat to human to determine the human equivalent dose (HED), a dose of 5 g/kg/day would be equivalent to 0.8 g/kg/day and a safety margin of 1.6. In dogs, the NOAEL of 3.75 g/kg/day represents a clinical safety margin of 7.5 based upon a MRHD of 30 g/day (0.5 g/kg/day for a 60 kg human). For information only, the HED from dog to human would be 2 g/kg/day, and a safety margin of 4.

Genotoxicity

RLY5016 has been found to be non-genotoxic when tested in-vitro and in-vivo. In-vitro testing included Ames and chromosomal aberration tests and in-vivo testing included a micronucleus test in rat bone marrow. The Ames bacterial cell mutation test concluded that there was no evidence of mutagenic effect.

The chromosomal aberration test using Chinese hamster ovary (CHO) cell cultures concluded that RLY5016 was not clastogenic with or without metabolic activation. The in-vivo genotoxicity of RLY5016 was evaluated in a rat bone marrow micronucleus test and did not significantly increase the frequency of micronuclei in polychromatic erythrocytes. Based on the completed studies, RLY5016 is considered non-genotoxic and non-clastogenic in these test systems.

Carcinogenicity

No carcinogenicity studies have been completed for RLY5016. This has been justified on the basis of the lack of systemic exposure as demonstrated in absorption data described in the PK section. In addition, there was no evidence of tumorigenic changes in the chronic animal studies over 6 or 9 month daily treatment. Given the lack of systemic absorption of RLY5016, the absence of carcinogenicity studies is acceptable.

Reproduction Toxicity

Male and female fertility and early embryonic development were studied in Sprague Dawley rats. Animals were orally administered RLY5016S in diet, at doses of 1, 2.5 and 5 g/kg/day. In male rats there were no significant changes to sperm number or motility, although there was a decrease in straight-line velocity at the high dose of 5 g/kg/day dose. This had no effect on fertility parameters. In female rats, there were no effects at any dose on pregnancy rates, implantation or foetal fertility compared to controls. The NOAEL was the highest dose tested, 5 g/kg/day for male and female rats. These findings are adequately reflected in section 4.6 and 5.3 of the SmPC.

Embryo-foetal development was studied in rats and rabbits. Pregnant female rats were treated with up to 6 g/kg/day in gestation day 6 to 17 via oral gavage. No drug-related effects were observed at any dose in treated females. There were no effects on litter sizes and no evidence of treatment-related variations or malformations. The NOAEL was determined as the highest dose tested, 6 g/kg/day. Similarly, non-adverse findings were observed in pregnant rabbits treated orally with up to 3 g/kg/day with RLY5016S. Two control animals died in the pivotal study, one due to unknown spontaneous death, and the other euthanized following signs of irregular and laboured respiration. The NOAEL in pregnant rabbits was the highest dose tested, 3 g/kg/day.

The wording in section 4.6 of the SmPC for pregnancy reflects the results of the non-clinical studies, and consider the lack of information from clinical exposure. Given the lack of human exposure data, the text reflects the need of caution for use of Veltassa during breastfeeding, i.e. a decision must be made whether to discontinue breast feeding or to discontinue/abstain from patiromer therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

The absence of peri/postnatal development studies has been adequately justified, and no juvenile toxicity studies have been completed.

Toxicokinetic data

No toxicokinetic data has been supplied for any study in either species. The absence of exposure data is justified given the lack of systemic exposure of RLY5016 as determined in the non-clinical PK studies.

Local Tolerance

No studies were provided to examine local tolerance, antigenicity, immunotoxicity, dependence or specific toxicological studies for metabolites. A detailed examination of actual/potential/theoretical impurities arising in the drug substance has been provided. Most of the identified PDEs and calculated drug substance specifications are acceptable with the exception of the derived specification for fluoride. Following reassessment of nonclinical, clinical and stability data, the applicant has proposed a new acceptable limit for fluoride which is likely to result in fluoride intake below the European Food Safety Authority limit of 7 mg/day. Safety assessments were provided in each instance and supportive in silico assessment using two models has been supplied. In addition, five impurities were assessed in GLP Ames assay to confirm non-genotoxicity. No concerns are raised in respect to impurities arising from the drug substance/manufacture. Adequate justification of levels of residual solvents and elemental impurities is supplied and there is sufficient justification for limits in the final drug product specification.

2.3.5. Ecotoxicity/environmental risk assessment

RLY5016S is a non-absorbed insoluble substance. Two aquatic effect studies were missing in the initial submission by the applicant. Thus, upon CHMP's request, these have been provided by the applicant during the evaluation phase. Following CHMP's assessment, the ERA for RLY5016S was finalised concluding that it is likely that the use of RLY5016S is not expected to pose a risk to the environment. In addition, the ERA for fluoride, based upon published literature, reveals no concerns for environmental risk.

Table 1. Summary of main study results

Substance (INN/Invented Name):					
Veltassa, RLY5016 (RLY5016A – active moiety, RLY5016S – active substance)					
PBT screening		Result		Conclusion	
Bioaccumulation potential- log K_{ow}		OECD107 or ...		N/A	
				Potential PBT (N/A)	
PBT-assessment					
Parameter		Result relevant for conclusion		Conclusion	
Bioaccumulation		log K_{ow}		N/A	
		BCF		N/A	
Persistence		DT50 or ready biodegradability		N/D, though not readily biodegradable	
Toxicity		NOEC or CMR		not T	
PBT-statement :		Due to the nature of the drug RLY5016S is not soluble in any media and PBT screening has not been performed			
Phase I					
Calculation		Value		Unit	
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)		126		µg/L	
		Refined: 12.6			
				> 0.01 threshold (Y)	
Phase II Physical-chemical properties and fate					
Study type		Test protocol		Results	
Adsorption-Desorption		Not performed		Not soluble in water and will be entirely associated with the solid phase	
Ready Biodegradability Test		OECD 301		6% degradation over 28 days	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems		OECD 308		N/D	
				N/D	
Phase IIa Effect studies					
Study type		Test protocol		Endpoint	
				value	
				Unit	
				Remarks	

Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC	15	mg/L	<i>Pseudokirchneriella subcapitata</i>
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC	3.1	mg/L	<i>Daphnia magna</i>
Fish, Early Life Stage Toxicity Test/ <i>Species</i>	OECD 210	NOEC	50	mg/L	<i>Pimephales promelas</i>
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	500	mg/L	
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO ₂	N/D		Not feasible to quantify RLY5016 degradation rates
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	320	mg/kg	
Terrestrial Plants, Growth Test/ <i>Species</i>	OECD 208	NOEC	500 125 500 500 32 500	mg/kg	Oats, Radish Lettuce Carrot, Tomato Onion
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	500	mg/kg	<i>Eisenia fetida</i>
Collembola, Reproduction Test	ISO 11267	NOEC	154	mg/kg	<i>Folsomia candida</i>
Sediment dwelling organism	OECD 218	NOEC	1000	mg/kg	<i>Chironomus riparius</i>

2.3.6. Discussion on non-clinical aspects

The non-clinical development programme for Veltassa consisted of a range of primary pharmacology, safety pharmacology, PK and toxicology studies, in which RLY5016 was given orally, the same route of administration as clinically used. Pharmacology studies demonstrated the ability of the polymer anion to bind potassium in the lumen of the colon and to increase potassium faecal excretion. Pharmacodynamic effects of Veltassa on serum potassium levels were observed in in vivo experiments performed in rats with normal renal function or a chronic renal failure model. In both in vivo experiments, an effect on the serum potassium levels was evident. The animals were fed a low calcium diet. In the study where no effect was seen on serum potassium levels in pigs, the animals appear to have been applied a normal production diet. However, the applicant has further discussed this and although a low calcium diet for rats was used, it did contain more than five times the recommended daily calcium intake for humans. Furthermore, the observed potential lack of efficacy may be due to the fact that studies were conducted in healthy animals and compensatory mechanisms involving decreased urinary potassium excretion prevented an impact on

serum potassium levels. In the clinical studies, efficacy on lowering serum potassium was demonstrated even when calcium levels were not controlled.

The applicant further discussed the implications of the reduced stomach emptying seen in the GI studies. This was in part due to the large quantity of the RLY5016 administered to rats. Following a detailed review of clinical data, it is concluded that this effect of reduced gastric emptying would have a limited impact to humans. The PK studies included absorption, distribution, metabolism and excretion characterisation and were performed in rats and dogs. The evidence supports a lack of RLY5016 bioavailability resulting in a lack of, or very limited systemic exposure.

Toxicity studies were conducted in rats and dogs (up to 26 and 39 weeks, respectively), including a full battery of genotoxicity studies, reproductive toxicity studies, and a detailed review of drug-related impurities. Due to the lack of systemic absorption, toxicokinetic determinations were not conducted in repeated-dose studies. Most of the toxicology studies, and all pivotal studies, were conducted according to GLP and reveal no target organ of toxicity.

The ERA for RLY5016S is acceptable. The use of RLY5016 is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical perspective, the applicant adequately addressed all points raised during the assessment and the CHMP considers the non-clinical development of Veltassa complete. The CHMP also considered that there are no further measures to be conducted in a post-marketing setting.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
PD	RLY5016-101	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 g/day ^b (multiple dose phase; as divided doses TID) Placebo (brown rice flour): (fixed dose TID)	Enrolled and Treated: 33 (25/8)	Healthy subjects	8 days (multiple dose phase)	Complete; CSR
PD	RLY5016-102	Assess the pharmacologic effects of TID, BID and QD dosing regimens	Open-label, randomized, multiple-dose, crossover	Fixed Dose: 30 g/day ^b (in TID, BID, QD dose regimens)	Enrolled and Treated: 12 (12/0)	Healthy subjects	18 days	Complete; CSR
PD	RLY5016-103	Evaluate the time to onset of potassium-lowering action of RLY5016 Powder for Oral Suspension	Open-label, single arm, multiple dose	Fixed Dose: 16.8 g/day ^c (as divided dose BID)	Enrolled and Treated: 25 (25/0)	Hyperkalemia and CKD	2 days	Complete; CSR
PD	RLY5016-201	Assess the PD effects of RLY5016 Powder for Oral Suspension on serum potassium in hyperkalemic subjects	Open-label, single arm, multiple-dose	Fixed Dose: 15 g/day ^b (as divided dose TID)	Enrolled and Treated: 6 (6/0)	Hemodialysis patients	7 days	Complete; CSR

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
Efficacy and Safety	RLY5016-301	Part A: Evaluate the efficacy and safety of RLY5016 Powder for Oral Suspension for the treatment of hyperkalemia Part B: Evaluate the effect of withdrawing RLY5016 Powder for Oral Suspension on serum potassium control, assess whether chronic treatment with RLY5016 Powder for Oral Suspension prevents recurrence of hyperkalemia and to provide placebo-controlled safety data	Part A: Single-blind, single-arm, RLY5016 for Oral Suspension treatment period, dose titration Part B: Single-blind, placebo-controlled, parallel group randomized withdrawal period	Starting Doses: 8.4; 16.8 g/day ^c (as divided doses BID) Titration Range: 0 – 50.4 g/day Placebo (MCC): (fixed dose BID)	Enrolled and Treated: Part A: 243 (243/0) Enrolled: Part B: 108 (55/53) Treated: Part B: 107 (55/52)	Hyperkalemia and CKD	Part A: 4 weeks Part B: 8 weeks	Complete; CSR
Efficacy and Safety	RLY5016-202	Evaluate the efficacy and safety of RLY5016 Powder for Oral Suspension for the prevention of hyperkalemia	Double-blind, placebo-controlled, parallel arm	Fixed Dose: 30 g/day ^b (as divided dose BID) Placebo (MCC): (fixed dose BID)	Enrolled: 120 (60/60) Treated: 105 (56/49)	Heart failure with or without CKD	28 days	Complete; CSR
Efficacy and Safety	RLY5016-205	Evaluate the efficacy and safety of RLY5016 Powder for Oral Suspension for the treatment of hyperkalemia Determine the optimal starting dose of RLY5016 Powder for Oral Suspension for Phase 3 Assess the long-term safety of RLY5016 Powder for Oral Suspension	Open-label, randomized, dose-ranging, dose titration	Starting Doses: 8.4; 16.8; 25.2; 33.6 g/day ^c (as divided doses BID) Titration Range: 0 – 50.4 g/day	Enrolled: 306 (306/0) Treated: 304 (304/0)	Hyperkalemia, CKD, type 2 diabetes, and hypertension	1 year (52 weeks)	Complete; CSR

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
Efficacy and Safety	RLY5016-204	Evaluate the efficacy and safety of RLY5016 Powder for Oral Suspension for the prevention of hyperkalemia and to evaluate the feasibility of individualized titration of RLY5016 Powder for Oral Suspension according to serum potassium	Open-label, single arm, dose titration	Starting Dose: 20 g/day ^b (as divided dose BID) Titration Range: 0 – 60 g/day	Enrolled and Treated: 63 (63/0)	CKD with heart failure	56 days	Complete; CSR
PK	RLY5016-104	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of amlodipine	Open-label, randomised, three-way crossover	Treatment A: amlodipine Treatment B: 25.2 g patiromer ^c coadministered with amlodipine Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after amlodipine	Enrolled and Treated: 15 (15/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-105	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of metoprolol	Open-label, randomised, three-way crossover	Treatment A: metoprolol Treatment B: 25.2 g patiromer ^c coadministered with metoprolol Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after metoprolol	Enrolled and Treated: 27 (27/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
PK	RLY5016-106	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of ciprofloxacin	Open-label, randomised, three-way crossover	Treatment A: ciprofloxacin Treatment B: 25.2 g patiromer ^c coadministered with ciprofloxacin Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after ciprofloxacin	Enrolled and Treated: 22 (22/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-107	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of lithium	Open-label, randomised, three-way crossover	Treatment A: lithium Treatment B: 25.2 g patiromer ^c coadministered with lithium Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after lithium	Enrolled and Treated: 16 (16/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-108	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of metformin	Open-label, randomised, three-way crossover	Treatment A: metformin Treatment B: 25.2 g patiromer ^c coadministered with metformin Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after metformin	Enrolled and Treated: 18 (18/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
PK	RLY5016-109	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of trimethoprim	Open-label, randomised, three-way crossover	Treatment A: trimethoprim Treatment B: 25.2 g patiromer ^c coadministered with trimethoprim Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after trimethoprim	Enrolled and Treated: 18 (18/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-110	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of clopidogrel	Open-label, randomised, three-way crossover	Treatment A: clopidogrel Treatment B: 25.2 g patiromer ^c coadministered with clopidogrel Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after clopidogrel	Enrolled and Treated: 51 (51/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-111	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of warfarin	Open-label, randomised, three-way crossover	Treatment A: warfarin Treatment B: 25.2 g patiromer ^c coadministered with warfarin Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after warfarin	Enrolled and Treated: 15 (15/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
PK	RLY5016-112	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of cinacalcet	Open-label, randomised, three-way crossover	Treatment A: cinacalcet Treatment B: 25.2 g patiromer ^c coadministered with cinacalcet Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after cinacalcet	Enrolled and Treated: 45 (45/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-113	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of furosemide	Open-label, randomised, three-way crossover	Treatment A: furosemide Treatment B: 25.2 g patiromer ^c coadministered with furosemide Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after furosemide	Enrolled and Treated: 40 (40/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d
PK	RLY5016-114	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of verapamil	Open-label, randomised, three-way crossover	Treatment A: verapamil Treatment B: 25.2 g patiromer ^c coadministered with verapamil Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after verapamil	Enrolled and Treated: 67 (67/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Dose(s) (Dosage Regimen)	No. Subjects ^a (Active/ Placebo)	Population	Treatment Duration	Study Status; Type of Report
PK	RLY5016-115	Evaluate the effect of RLY5016 Powder for Oral Suspension on the single-dose pharmacokinetics of levothyroxine	Open-label, randomised, three-way crossover	Treatment A: levothyroxine Treatment B: 25.2 g patiromer ^c coadministered with levothyroxine Treatment C: 25.2 g patiromer ^c 21 h before and 3 h after levothyroxine	Enrolled and Treated: 36 (36/0)	Healthy subjects	Treatment A: 1 day Treatment B: 1 day Treatment C: 2 days	Study conduct complete; PK Report ^d

BID = twice a day; CKD = chronic kidney disease; CSR = Clinical Study Report; h = hour; MCC = microcrystalline cellulose; No. = number; PD = pharmacodynamic; PK = pharmacokinetic; QD = once a day; TID = three times a day

a Includes all subjects enrolled in the study regardless of whether they received study drug.

b The dose is expressed as the amount of the calcium form of the polymer (RLY5016, also referred to as patiromer calcium) contained in each daily dose (e.g., 20 g/day RLY5016). To get to the equivalent dose of polymer anion (patiromer), these values have to be multiplied by 0.84.

c The dose is expressed as the amount of the polymer anion (patiromer) contained in each daily dose (e.g., 16.8 g/day patiromer).

d Completion of final CSR ongoing.

2.4.2. Pharmacokinetics

RLY5016 is a non-absorbed polymer; hence, no clinical PK studies have been conducted but descriptions of PK findings from preclinical models have been submitted.

Absorption, distribution, elimination

The extent of the bioavailability of the RLY5016 polymer was assessed in rats and dogs using ¹⁴C-labeled RLY5016. Plasma, faecal and urinary monitoring was conducted to assess possible absorption and distribution of the drug. The findings demonstrated the non-absorbed nature of the RLY5016 polymer and its lack of systemic bioavailability. Since the RLY5016 polymer is not systemically absorbed, metabolism of the compound does not occur in blood and tissues, and these were not evaluated for metabolites in non-clinical studies. One study was conducted that evaluated the metabolic stability of the RLY5016 polymer after recovery from human faecal samples. The physical stability of the RLY5016 beads during transit through the GI tract was demonstrated by recovering the test article from faecal samples collected in study RLY5016 101. The beads recovered from faeces remained as intact spheres.

The ex vivo potassium binding performance of the RLY5016 polymer was evaluated in an environment similar to that found in the human colon, where RLY5016 powder for oral suspension is expected to have its pharmacological effect. Human colonic and faecal matter was collected from three volunteers, and the soluble portion was isolated for use as a test medium in which to assess cation binding by RLY5016 or RLY5016Na (the polymer anion with calcium or sodium counter-ion, respectively). An assay concentration of 20 mg/mL RLY5016 was selected as an approximation of polymer concentration in the distal colon, assuming a 10-gram per day dose (equivalent to 8.4 g/day patiromer) and an average fluid load of 500 mL per day. The results indicate that RLY5016 powder for oral suspension is effective at removing potassium from an environment similar to that found in the human colon.

Dose proportionality and time dependencies

Dose proportionality was evaluated in Study RLY5016-101, a first-in-human, phase 1, randomised, double-blind, placebo-controlled, parallel-group, single- and multiple-dose escalation study of the safety and tolerability of RLY5016 in healthy adult volunteers. Eligible subjects were randomly assigned to 1 of 4 treatment groups in which 6 of 8 subjects per group received RLY5016 (1 g, 5 g, 10 g, or 20 g per dose) orally in suspension, and 2 of 8 subjects per group received matching placebo. For each treatment group, a single dose of RLY5016 or placebo was administered on day 1, followed by a 10-day observation and diet adjustment period. After acceptable single-dose safety and tolerability was determined, RLY5016 or placebo was administered TID on days 12 through 19 (8 days total). At least 7 days were allowed after single-dose administration at a particular dose level before progression to the next higher dose level.

RLY5016 increased potassium excretion, with statistically significant dose-dependent increases in mean faecal potassium excretion from baseline in the 5 g RLY5016 (617.2 mg, $p = 0.0195$), 10 g RLY5016 (1,069.7 mg, $p < 0.0001$), and 20 g RLY5016 (1,929.4 mg, $p < 0.0001$) TID groups compared with the placebo TID group. There was a corresponding decrease in urinary potassium excretion. Accordingly, the faecal/urinary potassium ratio also increased with increasing doses of RLY5016, with significant differences observed in the RLY5016 10 g TID group ($p < 0.01$) and 20 g TID group ($p < 0.0001$) compared with the placebo TID group. A dose-related increase in urinary and faecal calcium excretion was observed in all RLY5016 treatment groups.

A phase 1, open-label, single arm study (RLY5016-103) evaluated the time to onset of the potassium lowering action of RLY5016 powder for oral suspension. Subjects with CKD who had a serum potassium at

screening of 5.5 to 6.2 mEq/L and who were not on dialysis were entered into a 3-day in-patient run in period during which they began receiving a potassium and sodium controlled diet, followed by a 48 hour treatment period (fixed dose of 8.4 grams patiromer administered twice a day [BID] for 4 doses, administered at hours 0, 10, 24, and 34) during which serum potassium was assessed repeatedly. Subjects were required to be on a stable dose of at least one RAASi medication for 28 days prior to screening and, if taking antihypertensive medications, to be on a stable dose of that medication for at least 14 days prior to screening. The onset of the potassium-lowering action was defined as the earliest time point at which the least squares [LS] mean change from baseline in serum potassium was statistically significantly lower than 0 mEq/L at the given time point and at all later time points. From 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 ($p \leq 0.001$).

After the last dose at hour 34, mean serum potassium values continued to decline, reaching a mean (standard deviation [SD]) maximal reduction of 0.83 (0.454) mEq/L at 7 hours after the last dose (hour 41). At hour 58 (i.e., 24 hours following the last dose), the mean serum potassium was similar to that at the time of the last dose (mean [SD] serum potassium at hour 34: 5.28 [0.373] mEq/L; at hour 41: 5.11 [0.391] mEq/L; at hour 58: 5.27 [0.548] mEq/L).

Special populations

Subgroup analyses of the pooled data from Study RLY5016 301 and Study RLY5016 205 were performed for the following: age (< 65 years old and \geq 65 years old), gender, geographic region (US/EU countries and Non-EU countries), baseline body mass index (BMI) (< 30 kg/m² and \geq 30 kg/m²), baseline eGFR (< 30 mL/min/1.73 m² and \geq 30 mL/min/1.73 m²), presence/absence of heart failure, presence of diabetes mellitus and RAASi medications at baseline (1 medication and > 1 medication). Forest plots summarising these subgroup analyses for the two starting doses of RLY5016 powder for oral suspension (8.4 g/day patiromer, baseline serum potassium > 5.0 to 5.5 mEq/L) and (16.8 g/day patiromer, baseline serum potassium > 5.5 to < 6.0 mEq/L) showed that in all of these subgroups, serum potassium decreased statistically significantly from baseline, with results similar to those seen for the overall population.

Pharmacokinetic interaction studies

Since the RLY5016 polymer is not systemically absorbed, drug-drug interactions would arise through binding of the polymer to another orally administered drug in the GI tract leading to a change in absorption of the interacting drug. An in vitro test system was used to evaluate potential interactions between RLY5016S and 28 orally administered compounds commonly used in the target patient population for RLY5016. The in vitro binding studies were conducted in 3 different matrices simulating the conditions in different parts of the GI tract over a range of pH values. Tests were performed at the highest proposed clinical dose of RLY5016 and the lowest clinical dose of the test drug, representing the most extreme conditions for a drug-drug interaction. A binding of < 30% (equivalent to a test drug recovery of \geq 70%) was considered not clinically meaningful. Twelve of 14 drugs that demonstrated binding in vitro (at least 30% binding in at least one test matrix) were selected for testing in human drug-drug interaction studies (thiamine and quinidine were not tested).

The studies examined the effect of 25.2 g patiromer on single dose PK of the drug of interest using an open-label, randomized, 3-period, 3-way crossover, 3-sequence study design conducted in healthy volunteers. Healthy volunteer subjects were randomized to one of 3 treatment sequences, ABC, BCA, and CAB, where treatment A was the test drug administered alone, treatment B was test drug coadministered with RLY5016, and treatment C was test drug administered between two RLY5016 doses, i.e., 21 hours

after the first dose and 3 hours before the second RLY5016 dose. The no-effect criteria were 90% confidence intervals (CIs) for systemic exposure ratios within the range of 80 – 125%.

Based on the study findings, the following conclusions were made:

- Ciprofloxacin, levothyroxine, metformin and quinidine should be administered at least 3 hours before or after RLY5016.
- For untested active substances with a narrow therapeutic window, the clinical effect and adverse events should be monitored on initiation or dose adjustment of either RLY5016 or the concomitant medicinal product, or the physician should consider measuring blood levels. For these drugs, consider separating administration of RLY5016 by at least 3 hours.

Section 4.3 of the SmPC informs the prescribing physicians about the potential of drug-drug interactions.

Pharmacokinetics using human biomaterials

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action is the binding of potassium to patiromer, resulting in increased faecal potassium excretion and decreased serum potassium levels and this was studied in study RLY5016-201. The PD measurements assessed in this study were serum potassium and 24-hour faecal potassium excretion. Administration of RLY5016 15 g/day for 7 days resulted in a mean (\pm SD) decrease of 0.23 ± 0.33 mEq/L ($p = 0.14$) in pre-dialysis serum potassium concentration (Day 8 versus Day 1). The change from baseline to on-treatment (Days 2 to 8) in mean (\pm SD) daily serum potassium concentration was $-0.40 (\pm 0.44)$ mEq/L ($p = 0.08$). The effect of RLY5016 on mean daily serum potassium was not statistically significantly different whether on dialysis or not on dialysis; however, there was a numerically greater decrease in non-dialysis mean (\pm SD) daily serum potassium change from baseline (-0.45 ± 0.60 mEq/L, $p = 0.13$) compared with dialysis days (-0.33 ± 0.43 mEq/L, $p = 0.11$). The number of days that subjects had serum potassium levels in the normal range (≤ 5.5 mEq/L) was greater during the treatment period (67% of days) than the baseline period (36% of days). Treatment with RLY5016 15 g/day for 7 days resulted in a significant increase in mean (\pm SD) faecal potassium excretion of $359 (\pm 277)$ mg/day ($p = 0.02$).

Furthermore, study RLY5016 103 was conducted in 25 subjects with CKD who had serum potassium at screening of 5.5 to < 6.5 mEq/L. The onset of action, defined as the earliest time point at which the LS mean change from baseline in serum potassium was statistically significantly lower than 0 mEq/L at the given time point and at all later time points, was determined to be 7 hours. Also, this study contributed to the information regarding the duration of the serum potassium lowering effect after the discontinuation of dosing with RLY5016. The mean level of serum potassium at 24 hours post-dosing was similar to that at the time of the last dose.

Primary and secondary pharmacology

Patiromer is a non-absorbable cation-exchange polymer. Aside from lowering serum potassium it may also bind other cations such as magnesium, which are present in the GI tract. Excessive lowering of serum potassium, and potentially magnesium, may have physiological consequences that include signs and symptoms primarily impacting muscular or cardiac function. There are no known or expected

pharmacological properties on non-gastrointestinal organ systems such as the central nervous system, liver, endocrine, renal and hemodynamic systems beyond signs and symptoms related to the primary pharmacological effect of the drug on serum potassium and, to a lesser extent, on serum magnesium. The primary unwanted effects of RLY5016 are gastrointestinal in nature, primarily constipation and diarrhoea. Electrolyte disturbances associated with the primary pharmacologic action of the drug on serum potassium and magnesium have also been observed. These events are reflected in the SmPC.

2.4.4. Discussion on clinical pharmacology

The main site of action of patiomer is local in the gut, with no other systemic effects expected due to the non-absorbed nature of patiomer. The mechanism of action has been elaborated and it is conveyed by binding of patiomer to potassium in the gut and excretion of the complex in the faeces. This results in a lower body potassium concentration. Due to the action in the gut, the possibility of binding to other active substances is real as it has been demonstrated in the drug-drug interaction studies. For the majority of tested substances, there was no evidence of a clinically significant interaction with patiomer, indicating that a separation in dosing is not necessary for those drugs. However, given that patients taking patiomer are likely to be treated by multiple physicians, general dosing instructions may help to simplify use in clinical practice and reduce the potential for medication errors and interactions. For all drugs tested where the potential for an interaction with patiomer exists, a 3-hour separation between administration of the test drug and patiomer was sufficient to prevent an interaction. As such, the applicant revised section 4.5 of the SmPC to recommend administering any other oral medication at least 3 hours before or 3 hours after RLY5016. This recommendation has also been added to SmPC section 4.2. It is also stated as a prominent statement in section 2 of the PIL, as well as in the RMP.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered that the clinical pharmacology programme conducted by the applicant is sufficient for defining the clinical pharmacology of Veltassa. There are no measures necessary to address the issues related to pharmacology in the post-marketing setting. The SmPC and the RMP includes adequate information informing the prescribing physicians about the correct use of Veltassa and the appropriate implementation of risk minimisation measures particularly in the area of managing potential drug-drug interactions.

2.5. Clinical efficacy

The clinical programme for RLY5016 comprises twenty studies: three Phase 1 clinical pharmacology studies, twelve single dose drug-drug interaction studies, four Phase 2 studies and one two-part Phase 3 study. In clinical studies in patients with chronic kidney disease (CKD), heart failure (HF) or on haemodialysis, the duration of administration of study drug ranged from 48 hours to 52 weeks and the doses ranged from 8.4 to 50.4 g/day patiomer. The proposed dosing regimen for the marketed product is once daily up to a maximum dose of 25.2 g/day.

2.5.1. Dose response studies

Study RLY5016-205 : Multicentre, Randomised, Open, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the treatment of Hyperkalaemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone. The primary objective of the study was to determine the optimal starting dose of RLY5016 in treating hyperkalaemia in subjects with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI)

and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone. Secondary objectives were to determine the safety and efficacy of RLY5016 in treating hyperkalaemia in the above population and to evaluate the chronic use of RLY5016. The study had two treatment periods; firstly a treatment initiation period (TIP) lasting 8 weeks, followed by a Long-term Maintenance Period for an additional 44 weeks. Eligible subjects with screening serum potassium of 4.3 to 5.0 mEq/L and uncontrolled hypertension started a Run-in Period of 1 to up to 4 weeks in duration. During which Cohort 1 subjects discontinued pre-study RAASi medication and started losartan 100 mg. Spironolactone was added if necessary for additional blood pressure control. Cohort 2 subjects continued on their pre-study ACEI or ARB medication and added spironolactone to the regimen. Cohort 3 had serum potassium > 5.0 to < 6.0 mEq/L at screening or start of the Run-in Period and entered the TIP immediately while continuing to receive their current ACEI and/or ARB regimen. Subjects from all three cohorts were assigned to one of two strata according to baseline serum potassium:

- Stratum 1 (serum potassium values > 5.0 to 5.5 mEq/L) subjects were randomised to one of three RLY5016 starting doses: 8.4, 16.8, or 25.2 g/day patiomer
- Stratum 2 (serum potassium values > 5.5 to < 6.0 mEq/L) subjects were randomised to one of three RLY5016 starting doses: 16.8, 25.2, or 33.6 g/day patiomer

All RLY5016 doses were administered BID. Doses of RLY5016 were titrated based on individual subject response to achieve and maintain serum potassium in the range of 4.0 to 5.0 mEq/L during the 8-week TIP and in the range of 3.8 to 5.0 mEq/L during the 44 week LTMP. The dose of RLY5016 could be adjusted starting on Day 3 and up to the Week 51 Visit according to a titration algorithm that was designed to maintain serum potassium levels within a target range. An interim data analysis was performed based on data collected from 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. The mean change in central laboratory serum potassium from baseline to Week 4 (or prior to the initiation of RLY5016 dose titration, if occurs before Week 4) and its standard deviation (SD) for each starting dose group were calculated based on this interim data set. These interim results were used to determine the optimal starting dose of RLY5016 for each serum potassium stratum for future studies.

Diagnosis and Main Criteria for Inclusion: Men and women ages 30 to 80 years old who met the following criteria were eligible for the study:

- Diagnosed with T2DM after age 30 and treated with oral medication or insulin for at least 1 year prior to screening
- Had chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) 15 to < 60 mL/min/1.73m² at screening
- Had received an ACEI and/or ARB for at least 28 days prior to screening. Any subject with a history of hypertension must have had average systolic blood pressure (SBP) > 130 to ≤ 180 mmHg AND average diastolic blood pressure (DBP) > 80 to ≤ 110 mmHg (sitting) at screening. Whereas Cohorts 1 and 2 subjects must have had a diagnosis of hypertension to be enrolled in the study, Cohort 3 subjects without a history of hypertension could be enrolled.
- Had the following local serum potassium values:
 - Cohorts 1 and 2
 - At screening visit (S1): 4.3 to 5.0 mEq/L AND
 - At first Run-in Period visit (R0): ≤ 5.0 mEq/L (original protocol) or 4.5 to 5.0 mEq/L (Amendment 1) AND
 - At randomisation (baseline visit [T0]): > 5.0 to < 6.0 mEq/L Cohort 3
 - > 5.0 to < 6.0 mEq/L at S1 OR at R0 (after same day confirmation) • If in Cohorts 1 or 2 (non-hyperkalemic subjects who entered a Run-in Period), must have had:

- Urine albumin to creatinine ratio (ACR) \geq 100 mg/g (original protocol) or \geq 30 mg/g (Amendment 1) at S1 AND - Average urine ACR \geq 100 mg/g (original protocol) or \geq 30 mg/g (Amendment 1) at the beginning of the R0 based on up to three ACR values starting at S1 and ending at R0.

Test Product, Dose and Mode of Administration: RLY5016 was provided as a powder for oral suspension, comprising the drug substance, RLY5016S (the polymer anion and a calcium-sorbitol counterion complex and formulated with xanthan gum). RLY5016 was packaged in packets (4.2 grams patiomer per packet) and assembled as a kit for dispensing. Subjects were to take the drug orally in the morning and evening with meals and to mix study drug with water or a low-potassium food or drink prior to administration.

Losartan was provided from commercial supplies of 100mg tablets. Subjects in Cohort 1 were to take losartan orally once daily in the morning starting the morning after the R0 Visit of the Run-In Period. The dose remained at 100 mg/day throughout the study and could be taken for the duration of the study, including the follow-up period.

Spironolactone: 25 to 50 mg/day by mouth. Commercially available product (25-mg tablets). Subjects were to take spironolactone once daily. Spironolactone 25 mg/day was started on the morning following the R0 Visit (for non-hyperkalemic subjects assigned to Cohort 2) or on the day of the R2 Visit (for non-hyperkalemic subjects assigned to Cohort 1 who did not attain the blood pressure (BP) target of 130/80 mmHg). The dose could subsequently be increased to 50 mg/day before the T0 Visit in the TIP or during the LTMP. Spironolactone could be taken throughout the study, including the Follow-up Period.

Statistical Methods: Three populations were defined for analysis:

- Safety Population - all randomised subjects who received at least one dose of RLY5016.
- ITT Population - all subjects who were randomised to receive one of the three starting dose levels within each stratum and received at least one dose of RLY5016. The primary and secondary efficacy analyses were based on the ITT Population.
- PP Population - all subjects in the ITT Population who were compliant with RLY5016 defined as taking 80% to 120% of the dispensed dose, and who did not have any important protocol deviations. Sensitivity analyses of the primary endpoint analysis were based on the PP Population.

Parallel lines analysis of covariance (ANCOVA) models were used for the analysis of change from baseline of serum potassium levels at Week 4 and Week 8 within each stratum. The models included the treatment factor and baseline serum potassium value as the covariate. The least squares estimate of the mean change from baseline of each treatment and its 95% confidence interval (CI) were determined. A paired t-test was used to test whether the mean change from baseline in serum potassium was different from zero. A 95% CI of the pairwise difference between any two RLY5016 starting dose groups in the mean change of serum potassium was constructed. Time to events was analysed using the Kaplan-Meier method; the Fisher's exact test was used for comparisons of proportions. Statistical tests were performed at the alpha = 0.05 significance level. All tests were two-sided.

Study Endpoints: The primary efficacy endpoint was the mean change in serum potassium from baseline to Week 4 (or prior to titration of the RLY5016 dose, if it occurred prior to Week 4).

RESULTS OF STUDY RLY5016-205

Demography and subject disposition: Three hundred and six subjects were randomised of whom 304 received study treatment. A total of 266 subjects completed the 8-week TIP and 197 completed the one year study period. A majority of the 304 subjects were male (63%) and all were Caucasian with a mean (\pm SD) age of 66.3 \pm 8.61 years (range 37 to 80). In both strata, the highest percentages of subjects had screening CKD stages of Stage 3a, 3b, or 4 (based on screening eGFR results). Subjects in the Stratum 2 starting dose groups with higher mean serum potassium levels at baseline had lower mean eGFR at

study entry, and there were higher proportions of subjects with CKD Stage 4 or 5 in Stratum 2 compared with Stratum 1. All subjects had T2DM and hypertension.

Primary Efficacy Endpoint: The mean change from baseline in serum potassium at Week 4 or prior to dose titration was statistically significant for all dose groups within both strata ($p < 0.001$). The observed least square (LS) mean (SE) overall change at Week 4 in Stratum 1 was - 0.47 (0.039) mEq/L (- 0.35, - 0.51, and - 0.55 mEq/L for the 8.4, 16.8, and 25.2 g/day patiromer starting dose groups, respectively). The LS mean (SE) overall change in Stratum 2 was - 0.92 (0.075) mEq/L (- 0.87, - 0.97, - 0.92 mEq/L for the 16.8, 25.2, and 33.6 g/day patiromer dose groups, respectively).

Treatment Initiation Period: Mean decreases in serum potassium from baseline to all time points during the TIP (regardless of titration) were observed for each starting dose group within both strata, including at Day 3 following administration of approximately 4 doses of RLY5016. Throughout the entire TIP, the LS mean change from baseline in Stratum 2 were consistently larger than those in Stratum 1. The range of the LS mean (SE) change from baseline overall for Stratum 2 was -0.59 (0.048) mEq/L (Day 3) to -1.14 (0.051) mEq/L (Week 5) and for Stratum 1 was -0.29 (0.028) mEq/L (Day 3) to -0.66 (0.027) mEq/L (Week 5). At Week 4, the proportion of Stratum 1 subjects with serum potassium within the range of 4.0 to 5.0 mEq/L was 85.4% and for Stratum 2 was 72.6%, and at 8 weeks was 89.1% and 82.9%, respectively.

Long-Term Maintenance Period: Regardless of stratum or starting dose, mean serum potassium values were decreased from baseline at every time point during the LTMP. The mean change from baseline in serum potassium for Stratum 1 subjects at all LTMP time points was approximately -0.50 mEq/L, and the mean change from baseline for Stratum 2 subjects for the same time points was approximately -1.00 mEq/L. At Week 28, the proportion of Stratum 1 subjects with serum potassium within the range of 3.8 to 5.0 mEq/L was 89.0% and for Stratum 2 was 95.1%, and at 52 weeks was 85.5% and 89.8%, respectively.

Post-treatment Follow-up: Serum potassium values started to increase after treatment with RLY5016 was discontinued. At Days 3 and 7 of the Follow-up Period the mean (SD) change from the end of treatment was 0.22 (0.453) mEq/L ($n = 163$) and 0.29 (0.503) mEq/L ($n = 154$), respectively, for subjects in Stratum 1 and 0.29 (0.564) mEq/L ($N = 58$) and 0.46 (0.540) mEq/L ($n = 57$), respectively, for subjects in Stratum 2.

Based on a pre-planned interim analysis, the lowest effective dose in each stratum was selected as starting doses for Phase 3 in the absence of a clear dose-dependent response. For subjects with baseline serum potassium of 5.1 to < 5.5 mEq/L, the selected starting dose was 8.4 g/day patiromer, and for subjects with a baseline serum potassium of ≥ 5.5 to < 6.5 mEq/L the selected starting dose was 16.8 g/day patiromer.

Overview of change in serum potassium by dosage group and time data are mean (s.d.)

	Stratum 1 Serum K+ > 5.0 - 5.5 mEq/L			Stratum 2 Serum K+ > 5.5 - < 6.0 mEq/L		
	8.4 g/day n = 74	16.8 g/day n = 73	25.2 g/day n = 72	16.8 g/day n = 26	25.2 g/day n = 28	33.6 g/day n = 30
Baseline	5.14 (0.259)	5.17 (0.247)	5.14 (0.249)	5.70 (0.376)	5.68 (0.312)	5.61 (0.389)
Primary endpoint						
Change at Week 4	-0.35 (0.590)	-0.53 (0.650)	-0.54 (0.548)	-0.90 (0.637)	-0.98 (0.634)	-0.88 (0.930)
		P = 0.095 vs. low dose	P = 0.035 vs. low dose		P = 0.060 vs. low dose	P = 0.78 vs. low dose
	P < 0.001 for all comparisons vs. baseline			P < 0.001 for all comparisons		
Secondary endpoints						
Change at	-0.34	-0.49	-0.53	-0.91	-0.97	-0.87

Week 8	(0.599)	(0.668)	(0.602)	(0.664)	(0.653)	(0.955)
N Week 52	58	63	59	22	24	20
Change at Week 52	4.59 (0.429)	4.72 (0.380)	4.63 (0.376)	4.59 (0.464)	4.64 (0.358)	4.54 (0.447)

Study RLY5016-204: Multicentre, Open, Single-arm Study to Evaluate a Titration Regimen for RLY5016 in Heart Failure Patients with Chronic Kidney Disease.

Patients were enrolled at thirteen study centres in Georgia and Slovenia from May to September 2010. The primary objective of the study was to evaluate the feasibility of individualised titration of RLY5016 according to serum potassium (K⁺). The secondary objectives were to assess the effects of RLY5016 on serum potassium in heart failure (HF) subjects with chronic kidney disease (CKD) and to assess the safety and tolerability of RLY5016 HF subjects with CKD.

Methods: This was an open-label, single-arm study to evaluate a titration regimen for RLY5016 in subjects with HF and CKD (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²) receiving one or more of the following: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or beta blockers (BB). Following successful completion of screening and baseline (Day 0) evaluations, eligible subjects were enrolled in the study. On Day 1, subjects commenced treatment with RLY5016 10 g/day twice daily and spironolactone 25 mg/day once daily. Subjects were to receive RLY5016 for 8 weeks. Study visits were scheduled for Days 3, 7, 14, 21, 28, 35, 42, 49 and 56. A follow-up visit was to occur on Day 63 or 7 days after the last dose. At selected study visits, RLY5016 or spironolactone doses were adjusted according to a dosing algorithm designed to maintain each subject's serum potassium in the target range of 4.0 – 5.1 mEq/L. RLY5016 could be titrated up or down by 10 g/day to a minimum of 0 g/day or a maximum of 60 g/day. Spironolactone could be increased once to 50 mg/day, and no decreases were allowed. Any subject with a serum potassium value < 3.5 or > 5.5 mEq/L on two consecutive study visits despite dose titration was withdrawn from the study. During the 8-week treatment period, subjects were prohibited from taking polymer based drugs, other phosphate or potassium binders, potassium-sparing medications (i.e., potassium-sparing diuretics and other non-study aldosterone antagonists [AAs]), potassium supplements and intravenous cardiac medications. At each study visit, serum potassium efficacy assessments and safety assessments (e.g., adverse events and 12-lead electrocardiograms) were performed.

Inclusion criteria: Eligible subjects were at least 18 years of age, had a history of chronic HF, were clinically indicated to start spironolactone therapy, had a serum potassium measurement of 4.3 – 5.1 mEq/L at screening and baseline, had CKD with an eGFR < 60 mL/min/1.73 m² at screening based on serum creatinine and using the Modification of Diet in Renal Disease (MDRD) formula, and were taking one or more HF therapies (ACEIs, ARBs, or BBs). Women of childbearing potential must have been non-lactating, must have had a negative serum pregnancy test at screening, and must have used a highly effective form of contraception for at least three months before RLY5016 administration, during the study, and for one month after study completion. Male subjects and/or their female partners of child-bearing potential must have used a highly effective form of contraception during the study and for three months after study completion.

Exclusion criteria: a history of bowel obstruction, swallowing disorders, severe gastrointestinal disorders, or major surgery, uncorrected primary severe valvular disease, known obstructive or restrictive cardiomyopathy, or uncontrolled or hemodynamically unstable arrhythmia, an episode of unstable angina, a transient ischemic attack or stroke, or unresolved acute coronary syndrome within 2 months prior to baseline, recent (within 3 months prior to baseline) or anticipated need for cardiac surgery or intervention, heart or kidney transplantation or need for such transplantation during the study, receiving dialysis or anticipated need for dialysis during the study, sustained systolic blood pressure > 180 or < 90 mmHg; elevated liver enzymes (> 3 times the upper limit of normal), use of loop and thiazide diuretics

that had not been stable for at least 21 days prior to baseline, use of potassium sparing medication including AAs or potassium supplements in the last 21 days prior to baseline, or any condition within 30 days prior to baseline that had the potential to interfere with study compliance or jeopardise the safety of the subject.

Test Product, Dose and Mode of Administration: RLY5016 was supplied as a powder for oral suspension formulated with sorbitol, xanthan gum, silicone dioxide, yellow colour, titanium oxide and parabens packaged in sachets containing 5 g of RLY5016. Subjects were to take RLY5016 orally in the morning and evening with regular meals. Prior to administration, it was mixed with water, cranberry juice, or a low-potassium food. RLY5016 was initiated at a dose of 10 g twice a day and adjusted up or down by 10 g/day to maintain serum potassium in the target range of 4.0 – 5.1 mEq/L according to a pre-specified dosing algorithm. The minimum allowed dose was 0 g/day and the maximum allowed dose was 60 g/day. Subjects received RLY5016 for an 8-week treatment period (56 days).

In addition to RLY5016 subjects initiated treatment with spironolactone at a dose of 25 mg/day. Subjects were to take spironolactone orally once daily for 8 weeks. After Day 3, at the first occurrence of a serum potassium value of ≤ 5.1 mEq/L, the spironolactone dose was increased once to 50 g/day; dose reductions were not allowed.

Endpoints: The primary efficacy endpoint was the proportion of subjects with central laboratory serum potassium in the range of 3.5 – 5.5 mEq/L at the end of the study. Secondary endpoints were the percentage of subjects maintaining central laboratory serum potassium in pre-specified ranges (3.5 – 5.5 mEq/L and 4.0 – 5.1 mEq/L) by visit and during the treatment period; the mean dose of RLY5016 at the end of the study; the percentage of subjects requiring an up-titration or down-titration of the RLY5016 dose; the mean time to RLY5016 dose titration; mean number of RLY5016 titrations; RLY5016 dose by visit; the mean change from baseline in central laboratory serum potassium to the end of the study; the percentage of subjects discontinuing due to hyperkalaemia (serum $K^+ > 5.5$ mEq/L); the change in urine albumin to creatinine ratio (ACR) from baseline to Weeks 4 and 8 in subjects with a ACR of ≥ 30 mg/g at baseline; the percentage of subjects whose spironolactone dose could be increased to 50 mg/day.

Safety was assessed by the incidence and severity of treatment-emergent AEs, the incidence of clinically significant changes from baseline in clinical laboratory values (haematology, serum chemistry, urinalysis, and serum fluoride), the incidence of clinically significant changes from baseline in vital signs and ECG parameters, and the percentage of subjects who discontinued treatment with RLY5016 and spironolactone due to hypokalaemia (defined as a serum K^+ value < 3.5 mEq/L).

Statistical Methods: The study was to enrol approximately 60 subjects to ensure that at least 50 would receive RLY5016 and provide efficacy data for analysis. The sample size of 50 was not determined by formal sample size calculations; 50 subjects were considered appropriate based on the response to RLY5016 in prior studies. Data from all enrolled subjects who received RLY5016 and had available data were included in efficacy analyses.

For the primary efficacy variable, the proportion of subjects with central laboratory serum potassium in the range of 3.5 – 5.5 mEq/L at the end of the study and its 95% CI were calculated and summarised for all enrolled subjects who received at least one dose of study drug and who had at least one central laboratory post-baseline serum potassium value while on study drug or within one day after taking the last dose of study drug. Efficacy analyses were based on central laboratory values. The Clopper - Pearson method was used to calculate 95% binomial CIs for each of these percentages. No statistical hypothesis testing was conducted. Serum potassium data obtained more than one day after the last study dose was not used for the efficacy data analysis of the primary endpoint. Subgroup analyses were performed based on diabetes status, entry group (baseline serum $K^+ 4.3 - 5.1$ mEq/L and baseline eGFR < 60 mL/min, ages < 65 years and ≥ 65 years, ages < 70 years and ≥ 70 years, gender, BMI and country. Statistical

tests used for exploratory analyses of changes from baseline and subgroup differences in selected efficacy and safety parameters were performed at the $p = 0.05$ significance level. All tests were two sided.

RESULTS OF STUDY RLY5016-204

Subject Disposition, Demographics, and Baseline Characteristics: A total of 63 subjects were enrolled and received treatment, 56 (88.9%) completed the 8-week treatment period, and 7 (11.1%) prematurely discontinued from the study. The reasons for discontinuation were death 1 (1.6%) subject during treatment, AEs 4 (6.3%) subjects, serum $K^+ > 5.5$ mEq/L for two consecutive study visits, protocol violation 1 (1.6%) subject. Two additional deaths occurred 5 and 26 days after the last dose of RLY5016.

The 63 subjects had a mean age of 70.8 years, were all Caucasian, predominantly male 61.9%, and had a mean BMI of 28.6 kg/m^2 . All subjects had a history of HF (primarily ischemic 63.5%) with a mean duration of 3.9 years and characterised as New York Heart Association class II (46%) or III (54%). All subjects also had CKD (Stage 3a, 36.5%; Stage 3b, 41.3%; Stage 4, 7.9%); other comorbidities included hypertension (93.7%) and diabetes (42.9%). At baseline, subjects had a mean ejection fraction (EF) of 38.6%, the majority (52.4%) of whom had systolic dysfunction (EF < 40%), and a mean eGFR of $45.9 \text{ mL/min/1.73 m}^2$. The baseline mean central laboratory serum K^+ value was 4.78 mEq/L. All subjects were taking an ACEI, ARB or BB at baseline. No subject was taking triple therapy (ACEI, ARB, and BB).

Primary Efficacy Variable: RLY5016 administered at a starting dose of 20 g/day with individualised titration effectively controlled serum potassium levels that were within normal limits at baseline in subjects with HF and CKD who were started on spironolactone; 90.5% (95% CI 80.4%, 96.4%) of subjects had central laboratory serum potassium levels in the range of 3.5 – 5.5 mEq/L at the end of the 8-week study treatment period.

Secondary Efficacy Variables: The percentage of subjects maintaining central laboratory serum potassium within 3.5 – 5.5 mEq/L by visit ranged from 91.2% to 100%, and was 76.2% (95% CI: 63.8%, 86.0%) during the entire 8-week study treatment period. The percentage of subjects maintaining central laboratory serum potassium within 4.0 – 5.1 mEq/L by visit ranged from 72.6% to 90.3%, and was 30.2% (95% CI: 19.2%, 43.0%) during the entire 8-week study treatment period. The mean \pm standard deviation of on-treatment daily dose of RLY5016 was 22.5 ± 7.8 g. 33.3% of subjects required up-titration of RLY5016 at any time during the study. 12.7% of subjects required down-titration of RLY5016 at any time during the study. The median time (95%CI) to first RLY5016 titration was 21 (14.0, 36.0) days. The mean \pm SD number of RLY5016 titrations during the study was 1.3 ± 1.1 . The mean \pm SD RLY5016 daily dose by visit from Weeks 2 – 8 ranged from 21.7 ± 6.1 g to 23.0 ± 12.4 g. The mean \pm SD change in central laboratory serum potassium from baseline (4.78 ± 0.508 mEq/L) to the end of study was -0.13 ± 0.686 mEq/L. One (1.6%) subject was withdrawn from the study based on a pre-specified withdrawal criterion of two consecutive local laboratory serum K^+ values > 5.5 mEq/L despite a RLY5016 or spironolactone dose titration at the first of these two visits. Spironolactone doses were successfully up-titrated to 50 mg/day in all subjects by Day 14.

Overview of efficacy results Study 204

Endpoint	Result
Primary endpoint	
Proportion of subjects with serum potassium in the range of 3.5 – 5.5 mEq/L at end of study	57 of 63 (90.47%)
Secondary endpoints	
Percentage of subjects with serum potassium in the range of 3.5 – 5.5 mEq/L by visit and during the entire treatment period	48 of 63 (76.2%)
Percentage of subjects with serum potassium in the range of 4.0 – 5.1 mEq/L by visit and during the entire	19 of 63 (30.16%)

treatment period	
Mean daily prescribed dose of RLY5016 at end of study	22.52 g (s.d. 7.83 – range 8.5 to 43.9)
Percentage of subjects requiring RLY5016 up-titration	21 of 63 (33.3%)
Percentage of subjects requiring RLY5016 down-titration	8 of 63 (12.7%)
Mean time to first titration of RLY5016	26.4 days
Percentage of subjects discontinuing due to hyperkalaemia	1 (1.6%)

2.5.2. Main studies

The efficacy data for RLY5016 Powder for Oral Suspension are derived from five clinical studies:

- RLY5016-301 - “A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia.”
- 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 ARB 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.”

Studies 301 and 205 are considered “Treatment Studies” because subjects enrolled in these studies had elevated serum potassium at baseline, whereas Studies 202 and 204 are considered “Prevention Studies” because subjects in these studies had normal serum potassium at baseline, but were started concurrently on spironolactone and the investigational drug at the beginning of the study. Of the five studies, all used individualized dose titration, except for Study 103 and Study 202, in which a fixed dose was given.

Pivotal trial RLY5016-301

A two part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalaemia.

Methods

This was a single-blind study in patients with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) at least 15 mL/min/1.73m² and less than 60 mL/min/1.73 m² who were receiving a stable dose of at least one renin angiotensin aldosterone system inhibitor (RAASi). At the beginning of the study, subjects were required to be hyperkalaemic with serum potassium of 5.1 to < 6.5 mEq/L. The study consisted of two sequential parts: Part A was an assessment of 4 weeks of dosing with RLY5016 in the treatment of hyperkalaemia; Part B was a randomised, placebo-controlled, 8-week assessment of the withdrawal of RLY5016 conducted in those subjects with a baseline serum potassium at the beginning of Part A ≥ 5.5 mEq/L who responded to the 4 weeks of treatment with RLY5016.

Study Participants

Subjects who met eligibility criteria were assigned to one of two RLY5016 starting dose groups:

- Group 1 – Subjects with a Part A screening serum potassium of 5.1 to < 5.5 mEq/L were assigned to a starting dose of 8.4 g/day patiromer (4.2 g twice daily).
- Group 2 – Subjects with a Part A screening serum potassium of 5.5 to < 6.5 mEq/L were assigned to a starting dose of 16.8 g/day patiromer (8.4 g twice daily).

Part A

Eligible subjects were 18 – 80 years of age, had CKD (with eGFR \geq 15 mL/min/1.73 m² and < 60 mL/min/1.73m², calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or the Modification of Diet in Renal Disease (MDRD) equation and based on the local laboratory serum creatinine and were receiving a stable dose of at least one RAASi angiotensin converting- enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) or aldosterone antagonist (AA) for at least 28 days prior to screening. Subjects were required to be hyperkalaemic with a screening serum potassium of 5.1 to < 6.5 mEq/L.

Females of child-bearing potential were non-lactating, must have had a negative serum pregnancy test at screening and must have used a highly effective form of contraception for at least 3 months treatment, during the study and for 1 month after study completion.

Subjects were not eligible if they had any of the following; hyperkalaemia at screening that, in the opinion of the investigator, required emergency intervention, potassium-related ECG changes at screening, auto-immune related CKD, Type 1 diabetes or a haemoglobin A1c (HbA1c) measurement > 10.0% within the previous 6 months in subjects with type 2 diabetes mellitus (T2DM), hospitalisation for hyper- or hypoglycaemia in subjects with T2DM or for acute exacerbations of heart failure (HF) within the last three months, history of or currently diagnosed diabetic gastroparesis or history of bariatric surgery, confirmed systolic blood pressure (SBP) \geq 180 mmHg or < 110 mmHg or diastolic blood pressure (DBP) \geq 110 mmHg or < 60 mmHg at screening, symptoms associated with postural hypotension, anuria or history of acute renal insufficiency in the past three months, confirmed diagnosis or history of renal artery stenosis, New York Heart Association (NYHA) Class IV HF, uncorrected hemodynamically significant primary valvular disease, known obstructive or restrictive cardiomyopathy or uncontrolled or haemodynamically unstable arrhythmia, coronary artery bypass graft, percutaneous intervention or major surgery including thoracic and cardiac within three months prior to baseline or anticipated need during study participation, heart or kidney transplant recipient or anticipated need for transplant during study participation, cardiovascular or cerebrovascular events within 2 months prior to screening, body mass index (BMI) \geq 40 kg/m²; serum magnesium < 1.4 mg/dL at screening, liver enzymes (ALT/AST) > 3 times upper limit of normal, active cancer, currently on cancer treatment or history of cancer in the past 2 years, history of alcoholism or drug/chemical abuse within 1 year of screening, use of potassium supplements, bicarbonate or baking soda in the last 7 days prior to screening, potassium-altering chronic medications if doses had not been stable for at least 28 days prior to screening, current use of calcium acetate or calcium carbonate, lanthanum carbonate, sevelamer, sodium polystyrene sulfonate or calcium polystyrene sulfonate, colestevlam, colestipol, cholestyramine, drospirenone, potassium supplements, lithium, bicarbonate or baking soda, trimethoprim, tacrolimus or cyclosporine, use of any investigational product within 30 days or 5 half-lives prior to screening, prior participation in any study assessing the efficacy and safety of RLY5016, in the opinion of the investigator any medical condition uncontrolled systemic disease or serious intercurrent illness that would significantly decrease study compliance or jeopardise the safety of the subject.

Part B

To be eligible for Part B, subjects had to meet all of the following; baseline serum potassium at the beginning of Part A ≥ 5.5 mEq/L, completed the four weeks of dosing with RLY5016 in Part A, serum potassium 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 to 50.4 g/day patiromer at the Part A Week 4 visit, and still receiving treatment with a RAASi at the Part A Week 4 visit.

Treatments

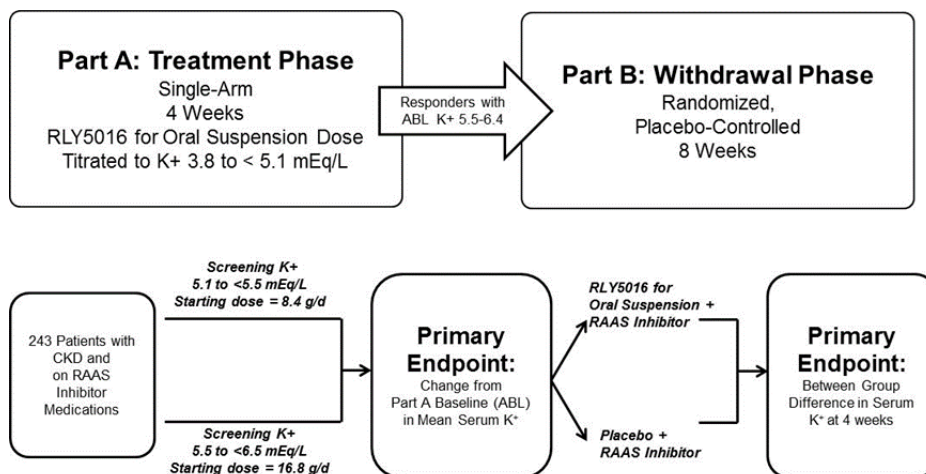
During Part A, the RLY5016 dose was titrated, if needed, based on the serum potassium level starting at Day 3 and continuing to the end of 4 weeks with the aim of achieving serum potassium in a target range of 3.8 to < 5.1 mEq/L. If a subject's serum potassium level was outside of the target range, RLY5016 dose titration was performed according to a protocol.

Part A titration algorithm. The RLY5016 dose could be titrated to a maximum of 50.4 g/day patiromer; the in increments of ± 8.4 g/day. If the serum potassium level was ≥ 6.5 mEq/L or if the serum potassium level was ≥ 5.1 mEq/L and the subject was receiving the maximum dose of RLY5016 patiromer the RAASi was to be stopped. Subjects who withdrew 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.

Part B was a randomised, placebo-controlled, 8-week assessment of the withdrawal of RLY5016. Subjects with a baseline serum potassium ≥ 5.5 mEq/L at the beginning of Part A were entered into Part B if they had responded to the 4 weeks of treatment with RLY5016 defined as completing Part A and satisfying all of the following at Week 4 visit; serum potassium in the range 3.8 to < 5.1 mEq/L, receiving a RAASi and receiving RLY5016 at a dose of 8.4 to 50.4 g/day. Subjects eligible for Part B were randomised 1:1 to either continue RLY5016 at the same daily dose or withdraw RLY5016 and receive placebo for an additional 8 weeks.

During Part B, RLY5016 (and RAASi) dose modification or discontinuation was performed according to protocol-specified titration algorithms based on serum potassium levels assessed starting at the Part B Day 3 visit and continuing through weekly visits to the end of the 8 week 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 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 was withdrawn. To help retain subjects in the study an intervention (increase in RLY5016 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 in increments of 8.4 g/day.

Depending on the serum potassium level, the Part B titration algorithms also specified 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 Part B 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. Depending on the serum potassium level, an additional Part B follow-up visit at 14 days after stopping RLY5016 was required. Part B follow up included the possibility of dose reduction or discontinuation of RAASi and the specification of standard care for hyperkalaemia if indicated based on the serum potassium level.



Objectives

Part A: To evaluate the efficacy and safety of patiromer for the treatment of hyperkalaemia.

Part B:

- To evaluate the effect of withdrawing patiromer on serum potassium control;
- To assess whether chronic treatment with patiromer prevents the recurrence of hyperkalaemia
- To provide placebo-controlled safety data.

Outcomes/endpoints

Part A: The primary efficacy endpoint for Part A was the mean change in serum potassium from Part A baseline to Week 4. Changes in serum potassium from baseline to other scheduled visits during Part A were also summarised but were not considered formal endpoints. The secondary efficacy endpoint for Part A was the proportion of subjects with a centrally measured serum potassium level that was in the Part A target range (3.8 to < 5.1 mEq/L) after 4 weeks of treatment.

Part B: The primary efficacy endpoint for Part B was the median change from Part B baseline serum potassium to serum potassium (central laboratory) at either:

- the Part B Week 4 visit, if the subject's serum potassium (local laboratory) 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 (local laboratory) was < 3.8 mEq/L or ≥ 5.5 mEq/L.

The secondary endpoints for Part B were: the proportion of subjects with a serum potassium ≥ 5.5 mEq/L at any time to Week 8, and the proportion of subjects with a serum potassium ≥ 5.1 mEq/L at any time to Week 8.

Sample size

The sample size of the study was planned in order to have at least 90% statistical power to detect a difference between RLY5016 for Oral Suspension and placebo with respect to the primary efficacy endpoint in Part B. Assuming a difference of 0.48 mEq/L between the RLY5016 for Oral Suspension and placebo groups in the mean change in serum potassium from Part B baseline to the Part B Week 4 visit and a standard deviation of 0.40 mEq/L in both the RLY5016 for Oral Suspension and placebo groups

(estimated based on data from subjects having received RLY5016 for Oral Suspension in previous study RLY5016-205), a sample size of 40 in each group in Part B was estimated to provide over 90% power. To ensure at least 40 subjects per group in Part B, Part A was planned to enrol approximately 240 subjects. With 240 subjects enrolled, Part A was estimated to have more than 99% power to detect a mean change from baseline in serum potassium ≥ 0.3 mEq/L. This estimate of statistical power was based on a two-sided one-sample paired t-test, significance level of 0.05 and the assumption of a standard deviation of 0.55 mEq/L (estimated based on baseline data from previous study RLY5016- 205).

Randomisation

Part A:

Not randomized.

Part B: a randomized withdrawal study; will enter subjects from Part A Week 4 Visit (AW4), ensuring equal distribution between placebo and active groups of subjects within each of the following four strata:

Part A baseline serum K+ from central laboratory	Type 2 diabetes mellitus	
	Yes	No
5.5- to < 5.8 mEq/L	Stratum a	Stratum b
≥ 5.8 mEq/L	Stratum c	Stratum d

The purpose of randomization at the beginning of Part B is to ensure balance of Part A baseline serum potassium and presence of diabetes in the two treatment groups. Subjects who meet the eligibility requirements will be randomized equally into the two treatment groups (patiromer and placebo) within each of the four stratification combination groups across all study sites.

Blinding (masking)

This is a single-blind study where the subjects were blinded to treatment assignment. Most investigational study staff were unblinded to treatment assignment (active during Part A and active versus placebo in Part B).

Statistical methods

The sample size was planned to have at least 90% statistical power to detect the difference between RLY5016 and placebo with respect to the primary efficacy endpoint in Part B. Sample size of 40 in each group in Part B was estimated to provide over 90% power. To ensure at least 40 subjects per group in Part B, Part A was planned to enrol approximately 240 subjects; Part A was estimated to have more than 99% power to detect a mean change from baseline in serum potassium ≥ 0.3 mEq/L. Randomisation in Part B was stratified to ensure equal distribution to the placebo and RLY5016 groups within the four strata formed by the combination of the following two baseline characteristics: (1) T2DM (yes/no), (2) Part A baseline serum potassium (< 5.8 mEq/L versus ≥ 5.8 mEq/L). For the primary efficacy endpoint of Part A, the mean change in serum potassium and 95% CI was estimated using a longitudinal repeated measures model of serum potassium from the Part A Week 1 visit to Week 4 visit. The model included two binary covariates, presence of heart failure (HF) at baseline and presence of T2DM at baseline and one continuous covariate, Part A baseline serum potassium. For the secondary efficacy endpoint of Part A, stratified estimates of the proportion, standard error (SE) and 95% CI were calculated with stratification by HF at baseline (yes/no), T2DM at baseline (yes/no) and Part A baseline serum potassium level (< 5.5 mEq/L versus ≥ 5.5 mEq/L).

For the primary efficacy endpoint of Part B, the two treatment groups were compared using an analysis of variance of the rank-transformed data that included factors corresponding to the four randomisation

strata. A Hodges-Lehmann estimate of the between-group difference (placebo – RLY5016) in median change in serum potassium was calculated and a 95% CI was constructed. The approach to ranking for the ANOVA accounted for values based on data prior to the Part B Week 4 visit by using the last observed rank carried forward. For each of the two secondary efficacy endpoints of Part B, the proportions in the two treatment groups were compared using a Mantel-Haenszel test stratified by the four randomisation strata; a Hochberg correction was used in assessing these two endpoints to ensure an overall Type I error rate of 0.05. Exploratory efficacy endpoints in Part B included the proportion of subjects who required protocol specified management of recurrent hyperkalaemia (i.e., RAASi dose reduction or discontinuation in the placebo group; patiromer dose increase or RAASi discontinuation in the RLY5016 group).

Analyses of the primary and secondary efficacy endpoints in Part A and Part B were based on all subjects who received at least one dose of investigational product, the intent-to-treat (ITT) population. Sensitivity analyses were performed to assess the robustness of the efficacy findings, including analyses based on per protocol populations (subjects with no important protocol deviations and subjects compliant with study drug). Subgroup analyses of efficacy by demographic and relevant baseline characteristics were also conducted.

Safety analyses included incidence of AEs with onset during Part A, incidence of AEs with onset during Part B by IP received (placebo or RLY5016) and incidence of AEs reported at any time during the study for those who continued into Part B. Analyses were also performed for SAEs, AEs considered by the investigator to be related to the IP and AEs leading to IP discontinuation or modification. Additional summaries presented events of interest, which included potassium-related ECG changes, serum potassium < 3.8 mEq/L, serum potassium \geq 5.5 mEq/L and selected types of AEs (e.g., renal events, those in the GI system and allergic reactions). Clinical laboratory test results (including serum magnesium, serum calcium and other electrolytes) were summarised descriptively over time and using standard shift tables. ECG changes were summarised, including shifts from normal to abnormal. Summaries of vital signs included mean changes in blood pressure over time and proportions of subjects with specified changes in blood pressure.

In Part A, the safety population was defined as all enrolled subjects who received at least one dose of RLY5016. In Part B, the safety population was defined as all randomised subjects who received at least one dose of randomised IP.

Results

Participant flow

A total of 243 subjects were enrolled in Part A; 92 (38%) had a screening serum potassium of 5.1 to < 5.5 mEq/L and were assigned to Dose Group 1 (starting dose of 8.4 g/day patiromer); 151 (62%) had a screening serum potassium of 5.5 to < 6.5 mEq/L and were assigned to Dose Group 2 (starting dose of 16.8 g/day patiromer). A total of 219 subjects; 92% of Group 1 and 89% of Group 2 completed the 4 weeks of Part A and 24 subjects 8% of Group 1 and 11% of Dose Group 2 withdrew early.

Of the subjects enrolled in Part A 58% were male and 98% were white. The median age was 65 years (range 29 to 80); 64% were enrolled in Eastern Europe/non-EU countries, 27% were enrolled in the EU and 9% were enrolled in the US. Based on eGFR 45% had Stage 4 CKD or worse (eGFR < 30), 26% had Stage 3b CKD (eGFR 30 to < 45), 20% had Stage 3a CKD (eGFR 45 to <60) and 9% had Stage 2 CKD (eGFR 60 to < 90). Overall, 57% of the subjects had T2DM, 42% had HF (65% were NYHA Class II), 25% had a prior MI and 97% had hypertension. Some differences between the starting dose groups were noted in baseline characteristics. The proportion of subjects with Stage 4 CKD or worse (43% in Dose Group 1 and 46% in Dose Group 2), time since CKD diagnosis (median of 3 years in Dose Group 1 and 2 years in

Dose Group 2), proportion of subjects with history of MI 21% in dose Group 1 and 27% in Dose Group 2 and time since diagnosis of MI (median of 8 years in Dose Group 1, and 2 years in Dose Group 2).

Of the 243 subjects enrolled in Part A, 121 (50%) either did not complete Part A or did not have a Part A baseline serum potassium ≥ 5.5 mEq/L and were therefore not eligible for Part B. Of the remaining 122 subjects, 110 (90%) met the criteria for having responded to RLY5016 during Part A. Three of the 110 elected not to participate in Part B; 107 subjects were randomised in Part B 52 to placebo and 55 to continue RLY5016. Of the 107 subjects in the Part B ITT population, 70% overall; 58% of the placebo group and 82% of the RLY5016 group completed the 8 weeks of dosing in Part B; 32 subjects 30% overall; 42% of the placebo group and 18% of the RLY5016 group withdrew early from Part B.

The placebo and RLY5016 groups were balanced with respect to baseline characteristics. Of the 107 subjects who participated in Part B, 54% were male and 100% were white. The median age was 65 years (range 32 to 80); 79% were enrolled in Eastern Europe/non-EU countries, 17% were enrolled in EU countries and 4% were enrolled in the US. Based on eGFR 41% of the Part B subjects had Stage 4 CKD or worse (eGFR < 30), 27% had Stage 3b CKD (eGFR 30 to < 45), 21% had Stage 3a CKD (eGFR 45 to < 60) and 11% had Stage 2 CKD (eGFR 60 to < 90). Overall, 63% of the subjects had T2DM, 46% had HF (65% were NYHA Class II), 30% had a prior MI and 97% had hypertension.

Recruitment

The study was conducted between 20 February 2013 (first subject enrolled) to 06 August 2013 (last subject completed last study visit).

Conduct of the study

The study was conducted at 71 centers in Croatia, Czech Republic, Denmark, Georgia, Hungary, Italy, Serbia, Slovenia, Ukraine, and United States from February to August 2013.

Baseline data

Part A: Eligible subjects were 18 - 80 years of age, had CKD (with eGFR ≥ 15 mL/min/1.73 m² and < 60 mL/min/1.73m², calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or the Modification of Diet in Renal Disease (MDRD) equation and based on the local laboratory serum creatinine) and were receiving a stable dose of at least one RAASi (angiotensin-converting-enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB] or aldosterone antagonist [AA]) for at least 28 days prior to screening. At the beginning of the study (i.e., to be eligible for Part A), subjects were required to be hyperkalaemic as evidenced by a screening serum potassium that was 5.1 to < 6.5 mEq/L (average of two values assessed by local laboratory). Females of child-bearing potential must have been non-lactating, must have had a negative serum pregnancy test at screening and must have used a highly effective form of contraception for at least 3 months before RLY5016 for Oral Suspension administration, during the study and for 1 month after study completion. All subjects provided written informed consent prior to participation in the study.

Part B: To be eligible for Part B, subjects had to meet all of the following: (1) baseline serum potassium (central laboratory) at the beginning of Part A ≥ 5.5 mEq/L, (2) completed the 4 weeks of dosing with RLY5016 for Oral Suspension in Part A, (3) 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), (4) receiving RLY5016 for Oral Suspension at a dose of 8.4 g/day to 50.4 g/day patiromer at the Part A Week 4 visit, and (5) still receiving treatment with a RAASi at the Part A Week 4 visit.

Numbers analysed

Part A: A total of 243 subjects were enrolled in Part A; 92 (38%) had a screening serum potassium of 5.1 to < 5.5 mEq/L and were assigned to Dose Group 1 (starting dose of 8.4 g/day patiromer); 151 (62%) had a screening serum potassium of 5.5 to < 6.5 mEq/L and were assigned to Dose Group 2 (starting dose of 16.8 g/day patiromer). A total of 219 subjects; 92% of Group 1 and 89% of Group 2 completed the 4 weeks of Part A and 24 subjects 8% of Group 1 and 11% of Dose Group 2 withdrew early. Of the subjects enrolled in Part A 58% were male and 98% were white. The median age was 65 years (range 29 to 80); 64% were enrolled in Eastern Europe/non-EU countries, 27% were enrolled in the EU and 9% were enrolled in the US.

Based on eGFR 45% had Stage 4 CKD or worse (eGFR < 30), 26% had Stage 3b CKD (eGFR 30 to < 45), 20% had Stage 3a CKD (eGFR 45 to <60) and 9% had Stage 2 CKD (eGFR 60 to < 90). Overall, 57% of the subjects had T2DM, 42% had HF (65% were NYHA Class II), 25% had a prior MI and 97% had hypertension.

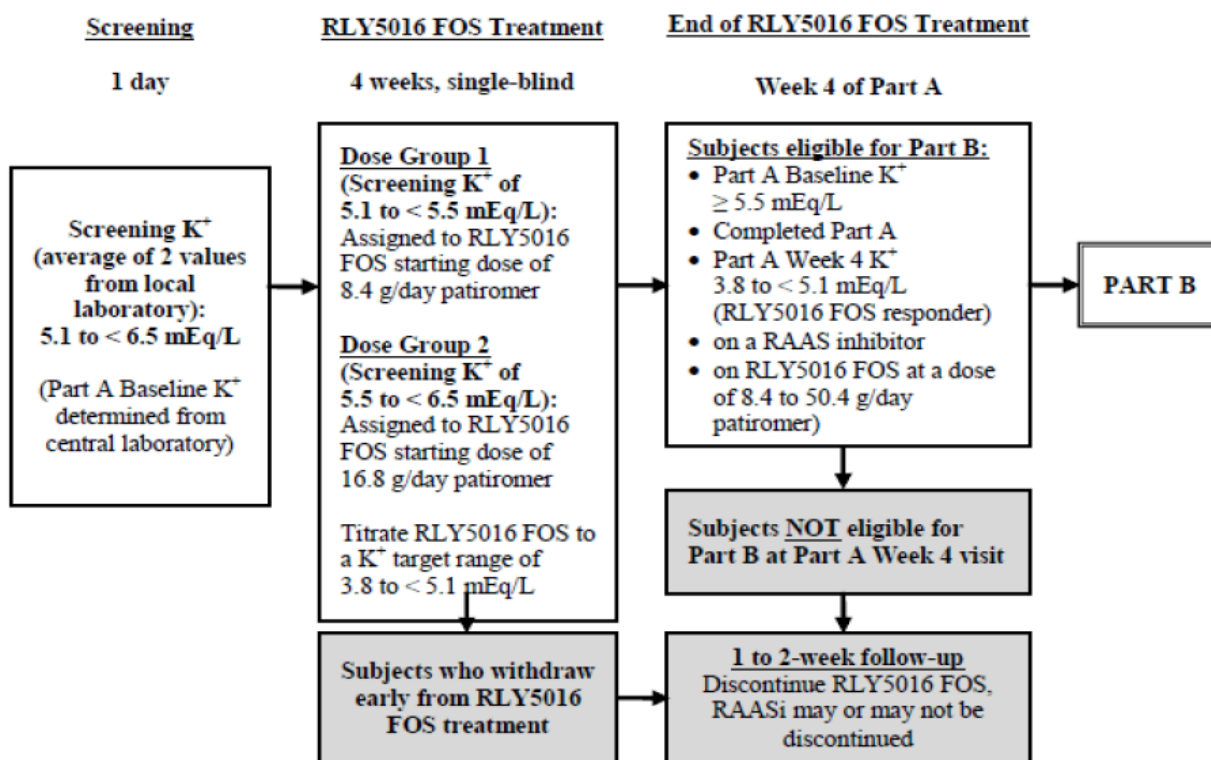
Some differences between the starting dose groups were noted in baseline characteristics. The proportion of subjects with Stage 4 CKD or worse (43% in Dose Group 1 and 46% in Dose Group 2), time since CKD diagnosis (median of 3 years in Dose Group 1 and 2 years in Dose Group 2), proportion of subjects with history of MI 21% in dose Group 1 and 27% in Dose Group 2 and time since diagnosis of MI (median of 8 years in Dose Group 1, and 2 years in Dose Group 2).

Part B: The 243 subjects enrolled in Part A, 121 (50%) either did not complete Part A or did not have a Part A baseline serum potassium \geq 5.5mEq/L and were therefore not eligible for Part B. Of the remaining 122 subjects, 110 (90%) met the criteria for having responded to RLY5016 during Part A. Three of the 110 elected not to participate in Part B; 107 subjects were randomised in Part B 52 to placebo and 55 to continue RLY5016. Of the 107 subjects in the Part B ITT population, 70% overall; 58% of the placebo group and 82% of the RLY5016 group completed the 8 weeks of dosing in Part B; 32 subjects 30% overall; 42% of the placebo group and 18% of the RLY5016 group withdrew early from Part B.

The placebo and RLY5016 groups were balanced with respect to baseline characteristics. Of the 107 subjects who participated in Part B, 54% were male and 100% were white. The median age was 65 years (range 32 to 80); 79% were enrolled in Eastern Europe/non-EU countries, 17% were enrolled in EU countries and 4% were enrolled in the US. Based on eGFR 41% of the Part B subjects had Stage 4 CKD or worse (eGFR < 30), 27% had Stage 3b CKD (eGFR 30 to < 45), 21% had Stage 3a CKD (eGFR 45 to <60) and 11% had Stage 2 CKD (eGFR 60 to < 90). Overall, 63% of the subjects had T2DM, 46% had HF (65% were NYHA Class II), 30% had a prior MI and 97% had hypertension.

Outcomes and estimation

PART A



Part A Primary Efficacy Endpoint Results

The mean (standard error [SE]) change in serum potassium from Part A Baseline to Part A Week 4 was -1.01 (0.031) mEq/L (95% CI: [-1.07, -0.95]); this mean reduction in serum potassium was statistically significantly different from zero (p < 0.001). This result satisfied criteria established with the FDA for the primary efficacy result to be considered pivotal (reduction from baseline in serum potassium of at least 0.7 mEq/L with p-value < 0.05). The mean change from baseline in serum potassium at Week 4 in Dose Group 1 (i.e., screening serum potassium of 5.1 to < 5.5 mEq/L) was -0.65 mEq/L (95% CI: [-0.74, -0.55]) and the mean change from baseline in serum potassium in Dose Group 2 (i.e., screening serum potassium of 5.5 to < 6.5 mEq/L) was -1.23 mEq/L (95% CI: [-1.31, -1.16]).

Phase 3 Study RLY5016-301 Part A Primary Efficacy Endpoint Results

	Starting Dose of RLY5016 PFOS		Overall Population (N=237)
	4.2 g Patiromer BID (N=90)	8.4 g Patiromer BID (N=147)	
	Serum Potassium (mEq/L)		
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 change from baseline mean ± SE (95% CI)	-0.65 ± 0.049 (-0.74, -0.55)	-1.23 ± 0.040 (-1.31, -1.16)	-1.01 ± 0.031 (-1.07, -0.95)

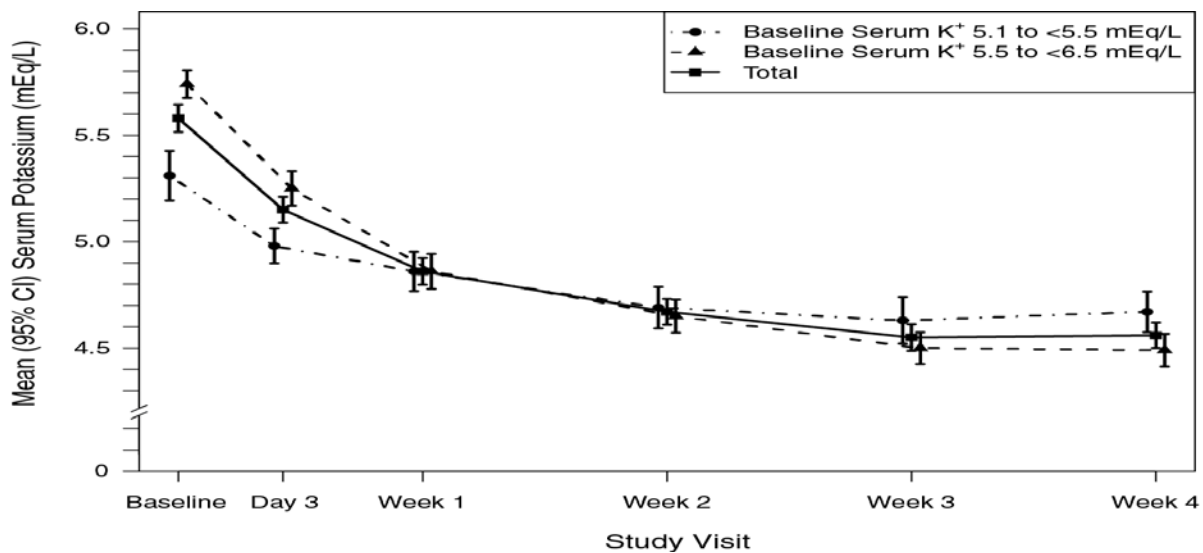
p-value	--	--	< 0.001
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Part A Secondary Efficacy Endpoint Results

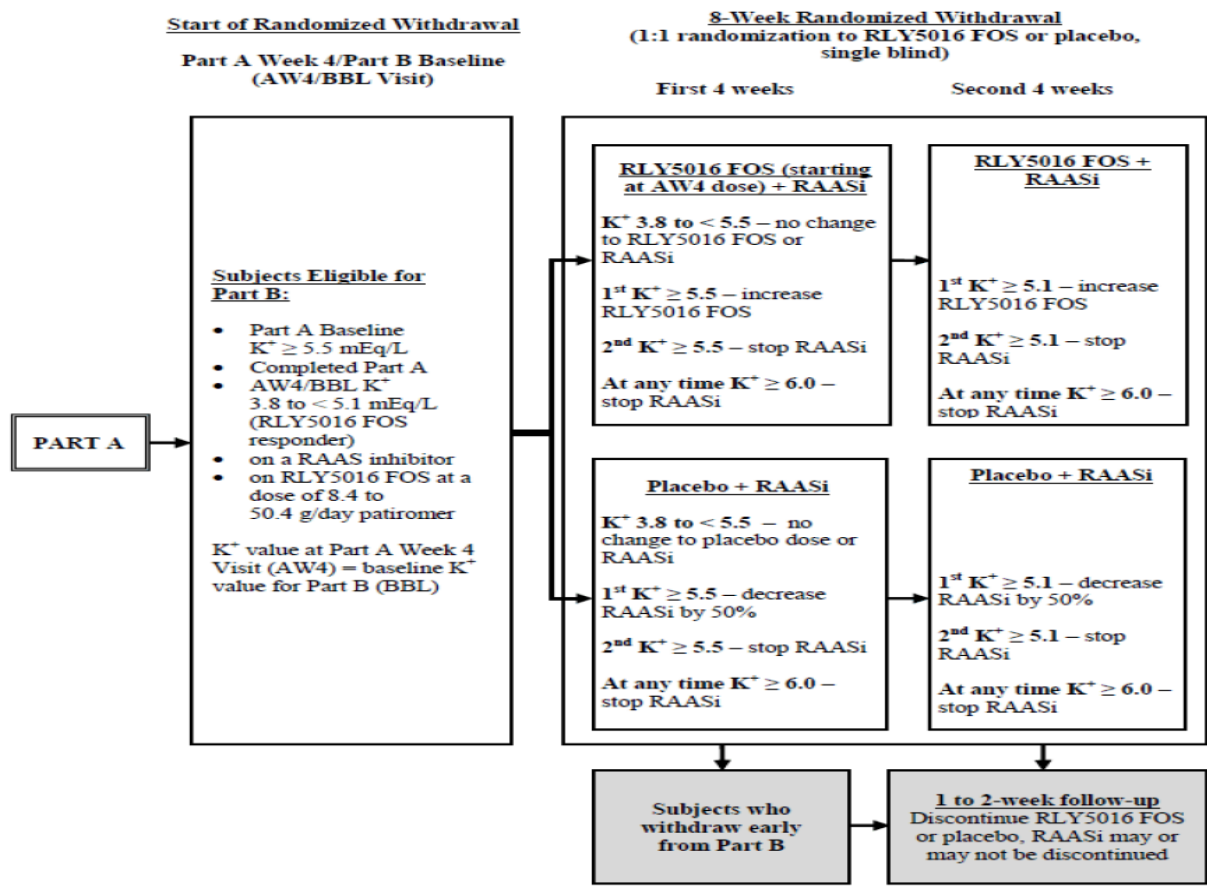
The proportion of subjects with a serum potassium level in the Part A target range of 3.8 to < 5.1 mEq/L at Week 4 was 76% (95% CI: [70%, 81%]). Similar percentages were observed in each starting dose group (Dose Group 1: 74%; 95% CI: [65%, 82%]; Dose Group 2: 77%; 95% CI: [70%, 83%]).

Part A Mean Serum Potassium over Time

Examination of mean serum potassium over time during Part A showed an overall mean change from baseline in serum potassium of -0.45 mEq/L by the Day 3 visit (i.e., approximately 48 hours after the start of dosing with RLY5016 Powder for Oral Suspension). For subjects in starting Dose Group 1, mean serum potassium was brought into the range of 3.8 to < 5.1 mEq/L at Day 3 (i.e., approximately 48 hours after the start of dosing), with mean serum potassium stabilizing within 2 weeks. For subjects in starting Dose Group 2, mean serum potassium was brought into the range of 3.8 to < 5.1 mEq/L by Week 1, with the mean serum potassium stabilizing by Week 3.



PART B



Part B Primary Efficacy Endpoint Results

The estimated difference in median change from Part B baseline (placebo minus RLY5016 Powder for Oral Suspension) was 0.72 mEq/L with 95% CI (0.46, 0.99); $p < 0.001$ for between-group difference in mean ranks of change. The estimated median change from Part B baseline in serum potassium in the placebo group was an increase of 0.72 mEq/L while the estimated median change from baseline in serum potassium in the RLY5016 Powder for Oral Suspension group was 0.00 mEq/L.

Phase 3 Study RLY5016-301 Part B Primary Efficacy Endpoint Results

	Placebo (N=52)	RLY5016 PFOS (N=55)	Difference	
			Estimate (95% CI)	p-value *
Estimated Median Change in Serum Potassium from Baseline (mEq/L)	0.72	0.00	0.72 (0.46, 0.99)	< 0.001

A significant result on the primary endpoint provides evidence that treatment with RLY5016 is beneficial in maintain serum plasma levels in responding patients. However, because of the design (with measurements not available after serum potassium goes outside the range 3.8 to < 5.5 mEq/L) the estimates of the size of the benefit are not considered fully reliable and should be treated with caution.

Part B Secondary Efficacy Endpoint Results

These secondary endpoints are more in line with the trial design (where patients were discontinued once serum potassium control was lost), and are considered to more accurately reflect the size of the treatment benefit. Additional analyses which evaluate the proportion of patients maintained within the acceptable range are required (three patients were over-treated, so fell below the lower bound of the 3.8 to < 5.5 mEq/L range and were forced to discontinue treatment, but they count as successes here).

Serum potassium ≥ 5.5 mEq/L at any time: The estimated proportion of subjects with a serum potassium ≥ 5.5 mEq/L at any time during the 8 weeks of Part B was 60% in the placebo group (95% CI of [47%, 74%]) and 15% in the RLY5016 Powder for Oral Suspension group (95% CI of [6%, 24%]); the estimated difference in percentages (placebo minus RLY5016 Powder for Oral Suspension) was 45% (95% CI of [29%, 61%]) and was statistically significant ($p < 0.001$).

Serum potassium ≥ 5.1 mEq/L at any time: As noted above, subjects were eligible for Part B if the Part A Baseline serum potassium was ≥ 5.5 mEq/L. The estimated proportion of subjects with a serum potassium ≥ 5.1 mEq/L at any time during the 8 weeks of Part B was 91% in the placebo group (95% CI of [83%, 99%]) and 43% in the RLY5016 Powder for Oral Suspension group (95% CI of [30%, 56%]); the estimated difference in percentages (placebo minus RLY5016 Powder for Oral Suspension) was 48% (95% CI of [33%, 63%]) and was statistically significant ($p < 0.001$).

Part B Time to Recurrent Hyperkalaemia

A time-to-event analysis was performed of the time to recurrent hyperkalaemia, defined to reflect the two threshold potassium levels that allowed for interventions to lower serum potassium during the first and second 4 weeks of Part B (i.e., serum potassium ≥ 5.5 mEq/L during Weeks 1 to 4 and serum potassium ≥ 5.1 mEq/L during Weeks 5 to 8). The estimated proportion with recurrent hyperkalaemia in the placebo group was higher than the estimated proportion in the RLY5016 Powder for Oral Suspension group within the first week of Part B and the difference between the treatment group proportions increased with time over Part B.

Study RLY5026-205

As described in section 2.5.1, study RLY5016-205 was a 1-year, open-label, randomized, Phase 2, dose ranging, efficacy and safety study in which 304 subjects with CKD and hyperkalaemia received RLY5016 Powder for Oral Suspension. In addition to the main dose ranging investigation purpose, several efficacy parameters were investigated. The study had two treatment periods: a Treatment Initiation Period for 8 weeks, followed by a Long-term Maintenance Period for an additional 44 weeks, allowing treatment with RLY5016 Powder for Oral Suspension for up to a total of 1 year. The main efficacy results are described below.

Primary Efficacy Endpoint Results: 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 both strata ($p < 0.001$). The LS mean (SE) change at Week 4 overall in Stratum 1 was -0.47 (0.039) mEq/L (-0.35, -0.51, and -0.55 mEq/L for the 8.4, 16.8 and 25.2 g/day patiromer starting dose groups, respectively), and the LS mean (SE) change overall in Stratum 2 was -0.92 (0.075) mEq/L (-0.87, -0.97, -0.92 mEq/L for the 16.8, 25.2 and 33.6 g/day patiromer starting dose groups, respectively).

Serum Potassium throughout the Study: Treatment Initiation Period (8 weeks): Mean decreases in serum potassium from baseline to all time points during the Treatment Initiation Period (regardless of titration) were observed for each starting dose group within both strata, including at Day 3 following administration of approximately four doses of RLY5016 Powder for Oral Suspension. Throughout the entire Treatment Initiation Period, the LS mean change from baseline in Stratum 2 (which had higher baseline serum

potassium levels) consistently were larger than those in Stratum 1. The range of the LS mean (SE) change from baseline overall for Stratum 2 was -0.59 (0.048) mEq/L (Day 3) to -1.14 (0.051) mEq/L (Week 5) and for Stratum 1 was -0.29 (0.028) mEq/L (Day 3) to -0.66 (0.027) mEq/L (Week 5). At Week 4, the proportions of Stratum 1 and Stratum 2 subjects with serum potassium within the range of 4.0 to 5.0 mEq/L were 85.4% and 72.6%, respectively; at Week 8, the proportions were 89.1% and 82.9%, respectively.

Long-Term Maintenance Period (44 weeks): Regardless of stratum or starting dose, mean serum potassium values were decreased from baseline at every time point during the Long-Term Maintenance Period. For both Stratum 1 and Stratum 2, the mean serum potassium level at all time-points during the Long-Term Maintenance Period was approximately 4.6 mEq/L, representing a mean decrease from baseline of approximately 0.50 mEq/L in Stratum 1 and a mean decrease from baseline of approximately 1.00 mEq/L in Stratum 2. At Week 28, the proportions of Stratum 1 and Stratum 2 subjects with serum potassium within the range of 3.8 to 5.0 mEq/L were 89.0% and 95.1%, respectively; at Week 52, the proportions were 85.5% and 89.8%, respectively.

Post-Treatment Follow-up: Serum potassium values started to increase after treatment with RLY5016 Powder for Oral Suspension was discontinued. At Days 3 and 7 of the Follow-up Period the mean (SD) change from the end of treatment with RLY5016 Powder for Oral Suspension was 0.22 (0.453) mEq/L (N = 163) and 0.29 (0.503) mEq/L (N = 154), respectively, for subjects in Stratum 1 and 0.29 (0.564) mEq/L (N = 58) and 0.46 (0.540) mEq/L (N = 57), respectively, for subjects in Stratum 2.

Ancillary analyses

No formal ancillary analyses of safety and efficacy have been performed.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial RLY5016-301

<u>Title:</u> A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia	
Study identifier	RLY5016-301

Design	<p>This was a single-blind study in subjects with chronic kidney disease (CKD) (with estimated glomerular filtration rate [eGFR] \geq 15 mL/min/1.73 m² and < 60 mL/min/1.73 m²) receiving a stable dose of at least one renin angiotensin aldosterone system inhibitor (RAASi). At the beginning of the study, subjects were required to be hyperkalemic with a screening serum potassium of 5.1 to < 6.5 mEq/L. The study consisted of two sequential parts:</p> <p>Part A was an open non-randomised 4-week treatment phase designed to evaluate the ability of RLY5016 to achieve a clinically meaningful reduction in serum potassium levels in subjects with hyperkalaemia due to chronic kidney disease.</p> <p>Part B, was a randomised, 8-week placebo-controlled, treatment withdrawal phase designed to evaluate the effect of withdrawing RLY5016 on serum potassium control, to assess whether RLY5016 prevented the recurrence of hyperkalaemia thereby assessing the need for chronic treatment.</p>	
	Duration of main phase:	Twelve weeks (4 + 8 Parts A and B)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	<p>Part A: Superiority over no-change intra-subject in serum potassium from baseline to Week 4</p> <p>Part B: Superiority over placebo change from Part B baseline to Week 4 (or earlier if potassium uncontrolled)</p>	
Treatments groups	Adult patients with hyperkalaemia due to chronic kidney disease	Part A starting dose was dependent on serum potassium: (1) if potassium 5.1 to < 5.5 mEq/L, 8.4 g/day patiromer (92 subjects) (2) If potassium 5.5 to < 6.5 mEq/L, 16.8 g/day patiromer (151 subjects)
	Adult patients with hyperkalaemia due to chronic kidney disease	Part B randomised to continuing RLY5016 (55 subjects) or switch to placebo (52 subjects)
Endpoints and definitions	Co-primary endpoint	Change from baseline in serum potassium
		Secondary endpoints were serum potassium as various study time points in the study number of patients with specified degrees of hyperkalaemia and hypokalaemia.
Database lock	30 th September 2013	
<u>Results and Analysis</u>		
Analysis description	Primary Analysis	

Analysis population and time point description	<p>Intent to treat</p> <p>Part A 243 subjects had a mean (standard error [SE]) change in serum potassium of -1.01 (0.031) mEq/L from baseline to Week 4.</p> <p>Part B 55 RLY5016 treated subjects had a median (quartiles Q1, Q3) change in serum potassium from Part B baseline to part B Week 4 of 0.00 (-0.30, 0.30) mEq/L and 52 placebo treated subjects had a median change of +0.72 (0.22, 1.22) mEq/L.</p>			
	variability statistic	Standard error see above.		
	endpoint	Change from baseline in serum potassium – see above.		
	Mean change in serum potassium (mEq/L) from Part A baseline to Part A Week 4	Mean	-1.01	
		SE	0.031	
		p-value	<0.001	
	Median change in serum potassium (mEq/L) from Part B baseline to Part B Week 4	Comparison groups	Part B: RLY5016 Part B: Placebo	
		Difference in Median Change	0.72 mEq/L	
		Quartiles (Q1, Q3)	(0.46, 0.99)	
		P value	<0.001	
Notes	<p>The study was almost entirely based on measurements of serum potassium, degrees of hyperkalaemia and hypokalaemia at various time points and proportion of patients experiencing them. Thus the endpoints are derivatives of one another. Neither urinary nor faecal potassium excretion was studied and levels of other important physiological ions were studied as safety endpoints.</p>			

Analysis performed across trials (pooled analyses and meta-analysis)

Repeated Measures Analysis of Central Laboratory Serum Potassium at Baseline and Endpoint (Week 4) by RLY5016 Powder for Oral Suspension Starting Dose (Full Analysis Set)

Visit Statistic	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	Study 205 N=73	Study 205 N=73	Study 205 N=26	Study 301 N=148	Study 205 N=28	Study 205 N=30
Baseline								
LS mean (SEM) ^b	5.15 (0.044)	5.32 (0.040)	5.17 (0.044)	5.14 (0.044)	5.70 (0.075)	5.74 (0.031)	5.68 (0.072)	5.61 (0.070)
95% CI ^b	5.06, 5.23	5.24, 5.40	5.08, 5.26	5.05, 5.23	5.55, 5.85	5.68, 5.80	5.53, 5.82	5.48, 5.75
p-value for comparing LS means within stratum/ within starting dose ^c	NA	0.003	NA	NA	NA	0.612	NA	NA
Endpoint (Week 4)								
LS mean (SEM) ^b	4.57 (0.050)	4.66 (0.045)	4.50 (0.049)	4.52 (0.049)	4.67 (0.095)	4.49 (0.040)	4.71 (0.092)	4.58 (0.092)
95% CI ^b	4.47, 4.66	4.57, 4.75	4.40, 4.59	4.43, 4.62	4.49, 4.86	4.41, 4.56	4.53, 4.89	4.39, 4.76
Change from baseline to endpoint (Week 4)								
LS mean (SEM) ^b	-0.64 (0.050)	-0.54 (0.045)	-0.70 (0.049)	-0.68 (0.049)	-1.04 (0.095)	-1.22 (0.040)	-1.00 (0.092)	-1.13 (0.092)
95% CI ^b	-0.73, -0.54	-0.63, -0.45	-0.80, -0.61	-0.78, -0.58	-1.22, -0.85	-1.30, -1.14	-1.18, -0.82	-1.32, -0.95
p-value for testing LS mean ^d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

ANOVA = analysis of variance; CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; NA = not applicable; SEM = standard error of the mean.

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.

Clinical studies in special populations

Subgroup analyses of the pooled data from Study RLY5016-301 and Study RLY5016-205 were performed for the following: age (< 65 years old and ≥ 65 years old), gender, geographic region (US/EU countries and Non-EU countries), baseline body mass index (BMI) (< 30 kg/m² and ≥ 30 kg/m²), baseline eGFR (< 30 mL/min/1.73 m² and ≥ 30 mL/min/1.73 m²), presence/absence of heart failure, presence of diabetes mellitus and RAASi medications at baseline (1 medication and > 1 medication). Subgroup analyses showed that in all of these subgroups, serum potassium decreased statistically significantly from baseline, with results similar to those seen for the overall population.

Supportive studies

Healthy Volunteer Studies

Study RLY5016-101: First-in-human, Phase 1, randomized, double-blind, placebo-controlled, parallel-group, single- and multiple-dose escalation study of the safety and tolerability of RLY5016 in healthy adult volunteers. Subjects were healthy adult males or females without a history of significant medical disease, 18 to 55 years of age, with screening body mass index (BMI) between 19 and 29 kg/m², serum potassium level > 4.0 and ≤ 5.0 mEq/L, and serum magnesium, calcium, and sodium levels within normal limits. Eligible subjects were randomly assigned to 1 of 4 treatment groups in which 6 of 8 subjects per group received RLY5016 (1 g, 5 g, 10 g, or 20 g per dose) orally in suspension, and 2 of 8 subjects per group received matching placebo. For each treatment group, a single dose of RLY5016 or placebo was administered on Day 1, followed by a 10-day observation and diet adjustment period. RLY5016 or placebo was administered TID on Days 12 through 19 (8 days total). At least 7 days were allowed after single-dose administration at a particular dose level before progression to the next higher dose level.

RLY5016 increased potassium excretion, with statistically significant dose-dependent increases in mean faecal potassium excretion from baseline in the 5 g RLY5016 (617.2 mg, $p = 0.0195$), 10 g RLY5016 (1,069.7 mg, $p < 0.0001$), and 20 g RLY5016 (1,929.4 mg, $p < 0.0001$) TID groups compared with the placebo TID group. There was a corresponding decrease in urinary potassium excretion. This normal homeostatic mechanism would be expected to maintain serum potassium in healthy volunteers following increased GI loss of potassium. Accordingly, the faecal/urinary potassium ratio also increased with increasing doses of RLY5016, with significant differences observed in the RLY5016 10 g TID group ($p < 0.01$) and 20 g TID group ($p < 0.0001$) compared with the placebo TID group. No clinically meaningful changes were apparent for urinary creatinine, chloride, sodium, and magnesium excretion or faecal magnesium and sodium excretion. No dose-related trend was apparent in serum potassium, magnesium, sodium, or calcium values.

Study RLY5016-102: Phase 1, open-label, multiple-dose crossover study to evaluate the pharmacology, safety, and tolerability of three RLY5016 dosing regimens in 12 healthy subjects. Subjects were adult males or females without a history of significant medical disease, 18 to 55 years of age, with screening BMI between 19 and 29 kg/m², serum potassium level > 4.0 and ≤ 5.0 mEq/L, and serum magnesium, calcium, and sodium levels within normal limits. Subjects were admitted to the clinic on Day -1 and remained in the clinic until discharge on Day 23. Subjects participated in a baseline period of 4 days during which they received a controlled diet. Each subject was then randomized to 1 of 6 crossover dosing sequences: ABC, ACB, BAC, BCA, CAB, or CBA (A = TID, B = BID, and C = QD dosing). RLY5016 was administered orally as an aqueous suspension of 30 g QD for 6 days, 15 g BID for 6 days, and 10 g TID for 6 days, for a total of 18 days. Subjects were required to consume a diet controlled for elemental potassium, calcium, sodium, and magnesium for the duration of the study.

Administration of 30 g/day RLY5016 led to mean (\pm standard deviation [SD]) increases in faecal potassium excretion of 1,550 (± 519), 1,419 (± 550), and 1283 (± 530) mg/day in the TID, BID, and QD dosing regimens, respectively. No statistically significant difference in mean daily faecal potassium excretion was observed among the TID/BID/QD regimens ($p = 0.37$). The corresponding, mean (\pm SD) decreases in urinary potassium excretion were 1,440 (± 384), 1,534 (± 295), and 1,438 (± 384) mg/day in the TID, BID, and QD dosing regimens, respectively; no statistically significant difference in mean urinary potassium excretion was observed among the three dosing regimens ($p = 0.39$).

Proof-of-Concept Study

Study RLY5016-201: Phase 2, open-label, multiple dose adaptive-design study to evaluate the PD effects of RLY5016 on serum potassium and to assess the safety and tolerability of RLY5016 in haemodialysis subjects. The study population consisted of male and female haemodialysis subjects between the ages of 18 and 70 years, with pre-dialysis serum potassium levels of at least 5.5 mEq/L on Day -7 during screening and on Day 1 of treatment. The study allowed for an up to 30-day Screening period (Day -30 to Day -1). On Day -8, eligible subjects were admitted to the Clinical Research Unit (CRU) and initially followed for 7 days without administration of RLY5016 (Days -8 to Day -1). Subjects were required to consume a potassium, magnesium, calcium, and sodium-controlled diet for the duration of the study. The diet was designed to provide a consistent amount of daily elemental potassium, magnesium, calcium, and sodium intake. In the initial (and only) treatment group, RLY5016 (5 g) was administered orally TID for 7 days (Days 1 to 7). Subjects were discharged on Day 8.

The study initially planned to enrol 12 to 24 subjects, but was terminated after the completion of 6 subjects due to difficulties enrolling subjects. Data from these 6 subjects were analysed. Administration of RLY5016 15 g/day for 7 days resulted in a mean (\pm SD) decrease of 0.23 ± 0.33 mEq/L ($p = 0.14$) in pre-dialysis serum potassium concentration (Day 8 versus Day 1). The change from baseline to on-treatment (Days 2 to 8) in mean (\pm SD) daily serum potassium concentration was $-0.40 (\pm 0.44)$ mEq/L ($p = 0.08$). The effect of RLY5016 on mean daily serum potassium was not statistically significantly

different whether on dialysis or not on dialysis; however, there was a numerically greater decrease in non dialysis mean (\pm SD) daily serum potassium change from baseline (-0.45 ± 0.60 mEq/L, $p = 0.13$) compared with dialysis days (-0.33 ± 0.43 mEq/L, $p = 0.11$). The number of days that subjects had serum potassium levels in the normal range (≤ 5.5 mEq/L) was greater during the treatment period (67% of days) than the baseline period (36% of days).

Treatment with RLY5016 15 g/day for 7 days resulted in a significant increase in mean (\pm SD) faecal potassium excretion of 359 (± 277) mg/day ($p = 0.02$). There was also a statistically significant increase in mean (\pm SD) faecal calcium excretion (1252 ± 290 mg/day, $p = 0.0001$), reflective of the amount of calcium intake associated with the study drug. There were no statistically significant differences in faecal excretion of sodium, magnesium, or phosphate.

Time to Onset of Action Study

Study RLY5016-103: Phase 1, open-label, single arm study to evaluate the time to onset of the potassium-lowering action of RLY5016 for Oral Suspension, and to evaluate its safety and tolerability in subjects with CKD and hyperkalaemia. Subjects were adult males or females 18 to 80 years of age with estimated glomerular filtration rate (eGFR) 15 to < 90 mL/min/1.73 m² and serum potassium of 5.5 to 6.2 mEq/L, and who were taking at least one RAASi medication. On the same day as Screening (Day R1), eligible subjects were admitted to the CRU for a 3-day in-patient diet run-in period (Days R1, R2, and R3). During this time, subjects received a controlled diet containing 60 mEq/day potassium and 100 mEq/day sodium, part of standard of care for managing CKD patients with hyperkalaemia. The first dose of RLY5016 Powder for Oral Suspension was administered immediately after the baseline blood sample was drawn and with the morning meal on Day T1 (Time 0). Subjects received 3 more doses of 8.4 g patiromer each with meals at 10, 24, and 34 hours after the initial dose, for a total of four doses. Subjects were discharged from the CRU on Day T3 (approximately 24 hours after administration of the last dose) and started an out-patient 6-day follow-up period, during which they attended two visits, F1 and F2, in 3 and 6 days after discharge from the CRU, respectively.

A total of 27 subjects were enrolled in the diet run-in period and of these, 25 subjects were treated and completed the study (2 subjects had exclusionary serum potassium results prior to dosing and were removed). The mean baseline serum potassium level was 5.93 mEq/L; 68% of subjects had baseline serum potassium levels ≤ 6.0 mEq/L, and the remainder (8 subjects, 32%) had levels > 6.0 mEq/L. All subjects had a history of CKD, with a mean duration of 4.5 years, and a majority of subjects were classified as either having Stage 3 (36%) or 4 (44%) CKD. Onset of action of RLY5016 for Oral Suspension, which was defined as the earliest time point at which the least squares (LS) mean change from baseline serum potassium value was statistically significantly < 0 mEq/L at the given time point and at all later time points, was determined to be 7 hours. Administration of four doses of 8.4 g patiromer resulted in a statistically significant reduction from baseline in LS mean serum potassium of 0.75 (0.063) mEq/L ($p < 0.001$) at Hour 48 from a Baseline mean of 5.93 mEq/L. After the last dose of RLY5016 Powder for Oral Suspension at Hour 34, mean serum potassium values continued to decline reaching a mean (SD) maximal reduction of 0.83 (0.454) mEq/L 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) of RLY5016 Powder for Oral Suspension (mean [SD] serum potassium at Hour 34: 5.28 [0.373] mEq/L; at Hour 41: 5.11 [0.391] mEq/L; at Hour 58: 5.27 [0.548] mEq/L).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Veltassa was been demonstrated in five clinical studies of the treatment (three studies) or prevention (two studies) of hyperkalaemia in subjects with CKD and/or heart failure. Treatment duration

ranged from 48 hours to 1 year. The trials enrolled and dosed 734 subjects with multiple common factors such as CKD and use of RAASi medications that contribute to hyperkalaemia. Most of the studies were single-blind, which can be considered acceptable since plasma potassium measurement is an objective measurement and not likely to be influenced by patient or physician knowledge of the given therapy. Most studies were placebo-controlled, there are no active-controlled clinical studies. The other main therapies for treatment of hyperkalaemia are sodium polystyrene sulfonate and calcium polystyrene sulfonate. Major limitations of these are tolerability and patient adherence, which limits their use to short durations. They are also contraindicated for patients with serum potassium < 5.0 mEq/L. Therefore it can be argued that due to the frequent stop and start cycles of drug administration which complicates chronic dosing, it would have been difficult to use them as comparators, particularly when evaluating long-term use.

Efficacy data and additional analyses

Primary and secondary outcomes were achieved and results were also supported by sub-population analyses.

Following administration of Veltassa, the onset of action was shown to be within 7 hours, and efficacy was persistent with continued dosing through at least 52 weeks, supporting the utility of Veltassa Powder for Oral Suspension as a treatment for both acute and chronic hyperkalaemia. Dosing and dose titration were well characterized in these trials and these data support the dosing recommendations for the product labelling. Across the five clinical studies, RLY5016 Powder for Oral Suspension demonstrated a consistent and reproducible potassium-lowering effect which enabled the majority of subjects to reach and/or remain in the target range with a low risk of hypokalaemia. The proposed starting dose is 8.4 g patiomer, which was the lowest starting dose evaluated in the clinical development program and was associated with statistically significant and clinically meaningful decreases in serum potassium levels. Starting treatment at the lowest effective dose, with titration up to 25.2 g/day patiomer, will result in the majority of patients achieving serum potassium concentrations in the target range while minimizing the risk of hypokalaemia. The pharmacodynamic profile of RLY5016 Powder for Oral Suspension supports a once daily dosing regimen, which will provide greater convenience for patients and enhance compliance. Once daily dosing will also allow flexibility in dosing times while observing a sufficient separation period (3 hours) between RLY5016 Powder for Oral Suspension and a potentially interacting concomitant medication. The ability to titrate RLY5016 Powder for Oral Suspension 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. The early onset of action, together with the persistence of effect over the long term, provide the necessary clinical data to support the effective use of RLY5016 Powder for Oral Suspension for the treatment of hyperkalaemia in both acute and chronic clinical settings.

The ability of Veltassa to enable spironolactone treatment was demonstrated in a randomised, double-blind, placebo-controlled study in heart failure patients who were clinically indicated to receive aldosterone antagonist. Patients initiated spironolactone at 25 mg/day at the same time as their randomised treatment, and were up-titrated to 50 mg/day after Day 14 if serum potassium was >3.5 and ≤ 5.1 mEq/L. Compared to placebo at the end of the 28-day treatment period, the Veltassa group experienced significantly lower serum potassium. Overall, the vast majority (99.4%) of patients in phase 2 and 3 clinical studies were receiving RAAS inhibitor therapy at baseline. Although the applicant proposed to reflect the concomitant use of RAASi and Veltassa in the clinical practice in section 4.1 of the SmPC, the CHMP did not support this. Instead, the benefit of Veltassa in the patients treated with RAASi is described in details in section 5.1 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Veltassa was demonstrated in both types of clinical studies - treatment (three studies) or prevention (two studies) of hyperkalaemia in subjects with CKD and/or heart failure. The dosing recommendation is supported by the studies; the once daily dosing is considered acceptable due to the need to minimise potential interactions with other medicinal products. Across all clinical studies, Veltassa demonstrated a consistent and reproducible potassium-lowering effect which enabled the majority of subjects to reach and/or remain in the target range with a low risk of hypokalaemia.

2.6. Clinical safety

The clinical programme for RLY5016 comprises eight studies: three Phase 1 studies, four Phase 2 studies and one two-part Phase 3 study. In clinical studies in patients with CKD, heart failure or on haemodialysis, the duration of administration of study drug ranged from 48 hours to 52 weeks and the doses tested ranged from 8.4 to 50.4 g/day patiromer providing a basis for assessing safety across a range of doses and for varying durations of use that could be applied to both the acute and chronic clinical settings of hyperkalaemia.

Patient exposure

A total of 791 subjects participated in the clinical studies with RLY5016 powder for oral suspension. Of these, 734 were exposed to at least one dose of RLY5016. The pooled safety population includes 666 subjects who received at least one dose of RLY5016 in studies RLY5016 202, RLY5016 204, RLY5016 205 and RLY5016 301 and 49 subjects who received at least one dose of placebo in study RLY5016 202. Of the 666 subjects, a total of 584 subjects were exposed to RLY5016 for \geq 4 weeks, 361 subjects were exposed for \geq 8 weeks, 219 subjects were exposed for \geq 6 months, and 149 subjects were exposed for \geq 1 year.

Adverse events

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were reported in 60.8% and 8.3%, respectively, of the pooled safety population receiving RLY5016 for up to 52 weeks, with a similar proportion in the treatment and prevention studies populations. Approximately 20% of subjects receiving RLY5016 experienced AEs considered related to study drug, but no SAEs were assessed by either the investigator or sponsor as related to the drug. Number of subjects discontinuing study drug due to an AE was relatively low at 9.0%, indicating the therapy was generally well tolerated, including by those who were treated for up to 1 year in study RLY5016 205. These trends were similar in the treatment and prevention studies.

Overall, the most common reported AEs ($>$ 5%) in the pooled studies were constipation, hypomagnesaemia and chronic renal failure. Additional AEs reported \geq 2% were diarrhoea, hypertension, anaemia, headache, hyperglycaemia, nausea, ventricular extrasystoles, abdominal discomfort, flatulence, hypoglycaemia, peripheral oedema, and supraventricular extrasystoles, and these AEs tended to be mild to moderate in nature. Many of the common events in the unpooled studies were similar to those observed in the pooled studies, and there were no deaths or reported SAEs in the unpooled studies.

Serious adverse event/deaths/other significant events

The relative proportion of subjects receiving RLY5016 who experienced SAEs was low at 8.3% in the pooled safety population. The System Organ Class (SOC) with the highest proportion of subjects reporting at least one SAE was cardiac disorders, 2.4%, and a similar incidence was observed in both the treatment and prevention Studies. The occurrence of cardiac-related SAEs was expected and consistent with the background cardiovascular history and risk factors of the studied population. No SAEs were considered related to study drug. There were four SAEs in the gastrointestinal SOC; two subjects experienced GI bleeding in the context of gastric ulcers with other predisposing risk factors and these events were not considered related to study drug. In the category of renal disorders, 1.1% of subjects experienced an SAE of renal failure chronic and 0.5% of subjects experienced a SAE of renal failure acute. The renal disorders SAEs reported were not considered drug-related.

There were 20 deaths reported in the clinical programme, all occurring in the pooled safety population. All deaths in the study were reviewed and adjudicated by an independent and blinded board. Nineteen of the deaths occurred in subjects receiving/received RLY5016 and a majority (15 subjects) of these deaths were adjudicated as cardiovascular in aetiology, with 10 of these deaths categorised as sudden cardiac death. In one death that occurred in a placebo subject in study RLY5016 202, the death was adjudicated as sudden cardiac death. None of the deaths that occurred, including CVS deaths, were considered by the SRB as related to hypokalaemia or hyperkalaemia.

Laboratory findings

Hypokalaemia occurred in a low frequency in the safety population, with 4.7% of subjects experiencing serum potassium values < 3.5 mEq/L and no subjects experienced a serum potassium value < 3.0 mEq/L. Changes in other ions such as Ca, Mg and fluoride were also minimal. Overall, in the RLY5016 clinical development programme, there was no indication of drug-related cardiac conduction or repolarization abnormalities.

Safety in special populations

Adverse events were analysed by subpopulations of interest including age, sex, BMI, geographic region, baseline potassium value, baseline eGFR and history of heart failure, myocardial infarction, or diabetes. In general, an increase in the frequency and incidence rate of AEs of interest occurred in subpopulations where the underlying condition is associated with an increased risk of those events (e.g., history of heart failure or myocardial infarction), confounding the interpretation and relationship with RLY5016. No new safety concerns were observed in elderly patients. Children were not included, and the product is indicated for adults only.

Safety related to drug-drug interactions and other interactions

The applicant has conducted a comprehensive panel of in vitro interaction studies and used them as a guide to which substances to study in vivo. Based on the results and due to the mechanism of action, drug interactions with oral medications were observed. These have been addressed by separating the dosing of these agents by a period of at least 3 hours as recommended in the SmPC. In addition, the SmPC of Veltassa has also been updated to include the dosing recommendation about the concomitant administration of Veltassa with other medicinal products. This is acceptable to the CHMP.

Discontinuation due to adverse events

In the pooled safety population, the AEs that led to permanent discontinuation of RLY5016 occurred in 60 subjects (9.0%), including 51 subjects (9.3%) treated with RLY5016 in the treatment studies and 9 subjects (7.6%) treated with RLY5016 in the prevention studies. The overall frequency for any one individual event leading to drug discontinuation was low (< 2%). This doesn't constitute a concern to the CHMP.

Post marketing experience

There is no post-marketing experience in the use of Veltassa, as declared by the applicant.

2.6.1. Discussion on clinical safety

The clinical development programme for RLY5016 included an evaluation of 791 subjects across eight studies including a two-part pivotal phase 3 study. The pooled safety population included 666 subjects who received RLY5016 (in studies RLY5016 202, 204, 205 and 301) and 49 subjects who received at least one dose of placebo (in study RLY5016 202); this safety population enabled an evaluation of safety in durations of treatment from 4 weeks to up to 52 weeks in a population with advanced CKD and heart failure and multiple comorbidities. In addition, a phase 1 study in 25 subjects with CKD and receiving RAASi therapy with baseline serum potassium levels from 5.5 to < 6.5 mEq/L provided an opportunity to further assess safety including serum potassium levels and AEs that occur in the hours to days following initiation of therapy in subjects with more severe hyperkalaemia. Furthermore, the safety evaluation also included an independent core ECG laboratory evaluation of ECG changes in studies RLY5016 301 and RLY5016 103 and an adjudication of all deaths by an independent SRB. Thus, the clinical development programme for RLY5016 provides a comprehensive evaluation of the safety of administering the drug in a diverse range of clinical settings and durations of treatment.

Overall, Veltassa appears to be well-tolerated in patients with underlying CKD, diabetes and/or heart failure, a population with a high burden of comorbidities and high prevalence of hyperkalaemia. The most common AEs (> 5% of subjects) reported in the pooled safety population were constipation, hypomagnesaemia and chronic renal failure. Importantly, the tolerability of the product in subjects with hyperkalaemia is underscored by the fact that a high proportion of subjects were able to remain on treatment for extended periods of time, as observed in the 52 week study RLY5016 205 (average duration of exposure was approximately 9 months). With treatment, there is a discernible pattern of AEs and safety findings across studies that could be considered as ADRs. These include constipation and diarrhoea, which appear to be self-limited and mostly mild in nature, as well as reduced levels of serum magnesium, leading to a low AE incidence of hypomagnesaemia. Other AEs of interest that occurred in the safety population receiving RLY5016 included cardiac related disorders, renal events and hypertension; however these findings are more likely related to underlying comorbid conditions, concomitant medications, intercurrent illnesses and progression of these comorbid diseases than a drug-related effect. Cardiac conduction disturbances were reported in a small proportion of subjects; however, ECG changes observed were not deemed to be related to hypokalaemia by the SRB and these changes likely reflect biological variability in a population who at baseline often had underlying derangements in cardiac conduction and underlying heart disease. An analysis of AEs by subgroup, while confounded by the underlying and associated comorbidities, showed that in general no trends were observed that suggest a risk profile different in one subgroup versus another. Deaths that occurred in the studies were predominantly cardiovascular in nature, were not considered related to study drug and were attributed to underlying cardiovascular conditions or risk factors. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of Veltassa can be considered acceptable and sufficiently described. The CHMP considers that there are no measures necessary to address issues related to safety.

2.7. Risk Management Plan

Table 6– Summary of the Safety Concerns

Important identified risks	<ul style="list-style-type: none"> Hypomagnesaemia / low magnesium
Important potential risks	<ul style="list-style-type: none"> Increased risk of intestinal perforation in patients with current or history of severe GI disorders Increased risk in patients with current or history of hypercalcaemia
Missing information	<ul style="list-style-type: none"> Pregnant and lactating women Treatment in patients <18 years old

Pharmacovigilance plan

There are no planned additional pharmacovigilance activities for this product.

Table 7 – Summary of the Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Hypomagnesaemia / Low magnesium	Wording in SmPC section 4.4, 4.8	None
Important potential risks		
Increased risk of intestinal perforation in patients with current or history of severe GI disorders	Wording in SmPC section 4.4	None

Increased risk in patients with current or history of hypercalcaemia	Wording in SmPC section 4.4, 5.1	None
Missing information		
Pregnant or lactating women	Wording in SmPC section 4.6, 5.3	None
Treatment in patients <18 years old	Wording in SmPC section 4.2	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 (dated 17 May 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21/10/2015. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of patiomer sorbitex calcium with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers patiomer sorbitex calcium to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Veltassa (patiromer sorbitex calcium) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hyperkalaemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with increased mortality risk. While rare in the healthy individuals with normal renal function, the prevalence of hyperkalaemia in patients with renal insufficiency or CKD ranges from 5% to 50% and increases as renal function declines. Thus, patients most at risk of hyperkalaemia are those with compromised renal excretion of potassium, primarily patients with CKD and/or patients being treated with drugs that inhibit renal potassium excretion,

3.1.2. Available therapies and unmet medical need

Sodium polystyrene sulfonate and calcium polystyrene sulfonate are two cation-exchange resins currently approved in the EU for the treatment of hyperkalaemia. They were introduced in the 1950s and 1960s; however, have not been rigorously studied. There are limited prospective, long-term clinical trial data available to understand the safety and efficacy of these agents. These products are not well tolerated and their use can be associated with life-threatening side effects including intestinal necrosis. Further, an appreciable sodium load can occur with sodium polystyrene sulfonate such that caution is advised when sodium polystyrene sulfonate is administered to patients who cannot tolerate even a small increase in sodium loads. These issues make the administration of sodium polystyrene sulfonate for prolonged durations of time difficult.

3.1.3. Main clinical studies

The safety and efficacy of Veltassa were demonstrated in a two-part, single-blind randomised withdrawal study that evaluated this treatment in hyperkalaemic patients with chronic kidney disease (CKD) on stable doses of at least one RAAS inhibitor (i.e. angiotensin-converting enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB] or aldosterone antagonist [AA]).

In Part A, 243 patients were treated with Veltassa for 4 weeks. Patients with a baseline serum potassium of 5.1 mEq/L to <5.5 mEq/L (mmol/L) received a starting dose of 8.4 g patiromer per day (as a divided dose) and patients with a baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L received a starting dose of 16.8 g patiromer per day (as a divided dose). The dose was titrated, as needed, based on the serum potassium level, assessed starting on Day 3 and then at weekly visits to the end of the 4-week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to <5.1 mEq/L). The

mean daily doses of Veltassa were 13 g and 21 g in patients with serum potassium of 5.1 to <5.5 mEq/L and 5.5 to <6.5 mEq/L, respectively.

In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to <5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor treatment were randomised to continue Veltassa or to receive placebo for 8 weeks to evaluate the effect of withdrawing Veltassa on serum potassium. In patients randomised to Veltassa, the mean daily dose was 21 g at the start of Part B and during Part B.

The Part B primary endpoint was the change in serum potassium from Part B baseline to the earliest visit at which the patient's serum potassium was first outside of the range of 3.8 to <5.5 mEq/L or to Part B Week 4 if the patient's serum potassium remained in the range.

The potential of Veltassa to enable concomitant RAAS inhibitor treatment was also assessed in part B.

The effect of treatment with Veltassa for up to 52 weeks was evaluated in an open-label study of 304 hyperkalaemic patients with CKD and type 2 diabetes mellitus on stable doses of a RAAS inhibitor.

3.2. Favourable effects

The clinical development programme demonstrated that Veltassa is effective in lowering serum potassium concentrations in patients with hyperkalaemia, mainly due to renal causes.

Results showed the mean change in serum potassium from Part A Baseline to Part A Week 4 was 1.01 mEq/L (95% CI: [-1.07, -0.95]); Group 1 0.65 mEq/L (95% CI: [0.74, 0.55]) and Group 2 1.23 mEq/L (95% CI: [1.31, 1.16]). After 4 weeks of treatment 76% (95% CI: 70%, 81%) of patients had a serum potassium in the target range of 3.8 mEq/L to <5.1 mEq/L.

In part B of the pivotal trial in patients who had responded to Veltassa the estimated proportion of subjects with a serum potassium \geq 5.5 mEq/L at any time during the 8 weeks of blinded treatment was 60% in the placebo group (95% CI of [47%, 74%]) and 15% in the Veltassa group (95% CI of [6%, 24%]); the estimated difference in percentages (placebo minus Veltassa) was 45% (95% CI of [29%, 61%]). This finding was statistically significant ($p < 0.001$) and is also considered clinically meaningful.

The potential of Veltassa to enable concomitant RAAS inhibitor treatment was also assessed in part B. Fifty-two percent (52%) of subjects receiving placebo discontinued RAAS inhibitor treatment because of recurrent hyperkalaemia compared with 5% of subjects treated with Veltassa. This is in details reflected in section 5.1 of the SmPC, in order to inform the prescribers about the possibility of concomitant use of RAASi with Veltassa.

The capacity to lower serum potassium levels was further supported by the results of a phase 2 dose-ranging trial with a long-term maintenance phase.

In an open-label study with patients with CKD and type 2 diabetes mellitus on stable doses of a RAAS inhibitor the effect of treatment with Veltassa for up to 52 weeks was evaluated demonstrating maintenance in decreases in serum potassium over 1 year of chronic treatment.

3.3. Uncertainties and limitations about favourable effects

The patients recruited in the clinical programme had chronic kidney disease; therefore the potassium lowering effects in cases of hyperkalaemia due to other reasons was not studied. However, considering the mechanism of action of Veltassa which is not specific to CKD this uncertainty can be considered negligible. Veltassa was also studied in a limited number of patients with estimated glomerular filtration

rate (eGFR) <15 ml/min/1.73 m² and patients receiving dialysis treatment. Further, there is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L as a precautionary measure this is outlined in the SmPC.

In the phase III study, patients were dosed twice daily, however, to mitigate the effects of potential binding to other oral medications, the advice in the SmPC is to dose once daily, which could potentially limit the effect of Veltassa when used in clinical practice.

3.4. Unfavourable effects

No major safety concerns were identified. From a safety perspective, the main concern is the binding of patiromer to other oral medications, thus limiting their absorption. This concern was sufficiently addressed by limiting the administration to once daily and to separate the intake by 3 hours from other oral medicinal products as outlined in the SmPC. There is also the risk of alterations in the concentrations of other ions such as magnesium (mild to moderate Hypomagnesaemia) and, as Veltassa contains calcium, the benefits and risks should be carefully evaluated in patients at risk of hypercalcaemia. This is sufficiently described in the product information for the attention of the prescriber.

The most common side effects are hypomagnesaemia, constipation, diarrhoea, abdominal pain and flatulence.

3.5. Uncertainties and limitations about unfavourable effects

The long-term safety database is limited. In the few patients that were dosed up to a year, efficacy was maintained and no safety issues were identified. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies. Gastrointestinal ischaemia, necrosis and/or intestinal perforation have been reported with other potassium binders. The benefits and risks of administering Veltassa would therefore need to be carefully evaluated in patients with current or history of severe gastrointestinal disorders, before and during treatment. These uncertainties are sufficiently addressed with routine risk minimisation measures.

3.6. Effects Table

Effects Table for Veltassa in the treatment of hyperkalaemia

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Lowering of Serum Potassium Levels	Change from baseline	mEq/L	Group 1, serum potassium of 5.1 to < 5.5 mEq/L started at a dose of 4.2 g patiromer BID; Group 2, serum	Single arm part A	Lack of active comparator Results showed the mean change in serum potassium from Part A Baseline to Part A Week 4 was 1.01 mEq/L (95% CI: [-1.07, -0.95]); Group 1 0.65 mEq/L (95% CI: [0.74, 0.55]) and Group 2 1.23 mEq/L	Study RLY501 6-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			potassium of 5.5 to < 6.5 mEq/L started at a dose of 8.4 g patiromer BID		(95% CI: [1.31, 1.16])	
Lowering of Serum Potassium Levels	Proportion of subjects with a serum potassium level in the Part A target range of 3.8 to < 5.1 mEq/L at Week 4	mEq/L	Same as above	Same as above	Overall 76% (95% CI: [70%, 81%]); Dose Group 1: 74%; 95% CI: [65%, 82%]; Dose Group 2: 77%; 95% CI: [70%, 83%]).	Study RLY5016 301
Effect of withdrawal of RLY5016 on potassium levels	Change in serum potassium from Part B baseline to the earliest visit at which the subject's serum potassium was first outside the range of 3.8 to < 5.5 mEq/L or to the Part B Week 4 visit if the subject's serum potassium remained in the range.	mEq/L	RLY5016 and RAASI dose modification or discontinuation was performed according to protocol-specified titration algorithms based on serum potassium levels	Placebo-control trial part B	The estimated difference in median change from Part B baseline (placebo minus RLY5016 Powder for Oral Suspension) was 0.72 mEq/L with 95% CI (0.46, 0.99); p < 0.001 for between-group difference in mean ranks of change.	Study RLY5016 301
Unfavourable Effects						
DDI	Test patiromer's potential to bind other oral medications <i>in vitro</i> .		The studies examined the effect of 25.2 g patiromer on single dose PK of the drug of	N/A	Of the 28 drugs that were tested in vitro, approximately half showed a positive interaction	DDI studies

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			interest using an open-label, randomized, 3-period, 3-way crossover, 3-sequence study design conducted in healthy volunteers.			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The favourable effects observed with Veltassa are considered important as currently there is an unmet need of safe and efficacious treatment for hyperkalaemia. With Veltassa, there is a statistically significant and clinically meaningful lowering of serum potassium levels, and on discontinuation of Veltassa, the levels tend to rise again. Although patients recruited in the clinical studies had CKD, which is the major reason for hyperkalaemia, similar effects of potassium lowering can be expected in cases of hyperkalaemia due to non-renal causes, based on the mechanism of action of patiromer. The ability to control potassium levels long term is particular considered an advantage in patients who are concomitantly treated with RAAS inhibitors as it may avoid their discontinuation in the context of recurrent hyperkalaemia. The risks of hypomagnesemia, hypercalcemia and GI side effects should be considered by the physician when deciding on treatment with Veltassa.

3.7.2. Balance of benefits and risks

Hyperkalaemia can result in muscle weakness, paralysis, life-threatening effects on cardiac conduction (e.g., QRS widening), arrhythmias such as ventricular fibrillation and sudden death and the benefits of lowering potassium levels in patients with conditions leading to Hyperkalaemia are to prevent these serious conditions.

Furthermore long term control of serum potassium levels may facilitate concomitant medication needed for patients with CKD hypertension, and congestive heart failure.

These advantages are balanced against the relatively benign safety profile of Veltassa.

The benefit-risk balance of using Veltassa for the treatment of hyperkalaemia in adult patients is therefore considered positive.

3.8. Conclusions

The overall B/R of Veltassa is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Veltassa is favourable in the following indication:

Treatment of hyperkalaemia in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Patiromer sorbitex calcium is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.