09 November 2023
EMA/534744/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Veltassa

International non-proprietary name: Patiromer

Procedure No. EMEA/H/C/004180/X/0031/G

Note

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

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List of abbreviations

AE adverse event

CI confidence interval

CKD chronic kidney disease

CRO Contract Research Organisation

DSMC Drug Safety Monitoring Committee

ECG electrocardiogram

eCRF electronic Case Report Form

eGFR estimated glomerular filtration rate

EU European Union

GI gastrointestinal

HK Hyperkalaemia

ICF Informed Consent Form

ICH International Council for Harmonisation

IEC Independent Ethics Committee

IQR interquartile range

IRB Institutional Review Board

IWRS interactive web response system

LT long-term

MedDRA Medical Dictionary for Regulatory Activities

PD pharmacodynamic

PIP Paediatric Investigational Plan

PT preferred term

QD once daily

SAE serious adverse event

SAP Statistical Analysis Plan

SD standard deviation

SMC Study Management Committee

SOC system organ class

TEAE treatment-emergent adverse event

US United States

1. Background information on the procedure

1.1. Submission of the dossier

Vifor Fresenius Medical Care Renal Pharma France submitted on 9 November 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new strength (1 g powder for oral suspension), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of population from 6 to 18 years old for Veltassa based on final results from paediatric study RLY5016-206P (EMERALD); this is a phase 2, open-label, multiple dose study to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer for oral suspension in children and adolescents 2 to less than 18 years of age with chronic kidney disease and hyperkalaemia. As a consequence, sections 1, 2, 4.1, 4.2, 4.8, 4.9, 5.1 and 6.5 of the SmPC were proposed to be updated. The Package Leaflet and Labelling are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) and (d) - Extensions of marketing authorisations

And Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0367/2021 on the agreement of a paediatric investigation plan EMEA-001720-PIP01-14-M02.

At the time of submission of the application, the PIP P/0367/2021 was not yet completed as some measures are deferred. The agreed PIP includes the following studies:

- Study 1 – Open-label study to evaluate dose, safety, and tolerability of patiromer calcium in children from 6 years to less than 18 years of age with hyperkalaemia due to chronic kidney disease. (RLY5016-206P; forms the basis of this submission)
- Study 2 – Single-blind dose titration study to evaluate efficacy and safety of patiromer calcium in the treatment of hyperkalaemia in children from 2 years to less than 18 years of age with chronic kidney disease. (RLY5016-305P) – ***deferred.***
- Study 3 – Open label, multiple-dose, safety and pharmacodynamic study in children from birth to less than 6 years of age with hyperkalaemia. (RLY5016-207P) – ***deferred.***
- Study 4 – Extrapolation study to support dosing and efficacy of patiromer calcium for oral suspension to the paediatric population.

The dates of completion for studies 2 and 3 are both deferred and will be the subject of later regulatory procedures.

The PIP has been modified three times since its initial agreement.

Modification 1 concerned a change from body surface area-based dosing to weight-based dosing.

Modification 2 related to a change in the design of Studies 1 and 3 to allow data patients from 6 to 18 to be accepted for MAA submission, in order to assess the efficacy and safety of patiromer, in conjunction with a Pop PD extrapolation study. This followed on from an acceptance by the PDCO that the applicant had experienced significant difficulties in recruiting patients to study 1, and that the data currently available could, if supported by a suitable extrapolation study, be sufficient to demonstrate efficacy and safety in children from 6 to 18 years, given the mechanism of action of the active substance.

Modification 3 related to update of studies 2 and 3, deletion of the extrapolation study 4 and replacement of this with a modelling and simulation study. Change to study 2 was to base the dose on results of study 1 and 3, rather than just on study 1. Change to study 3 was to determine the primary endpoint at Day 28 rather than at Day 14.

During assessment of this procedure, the applicant revised the originally sought indication to adults and adolescents aged 12 to 17 years. The applicant plans to further investigate the use of patiromer in patients from 6 to <12 years and proposes to amend the protocol of study 3 (EMERALD 2) for this purpose. This change will allow to further characterise the benefit/risk balance of Veltassa in patients from 6 to <12 years of age. The applicant intends to amend the protocol for study 3 to add an additional cohort in patients from 6 to <12 years of age with a minimum of 9 additional patients. Based on this, the total number of patients from 6 to <12 years for whom data would be available would be 18 patients (9 from study 3 and 9 from study 1). Further considerations of CHMP regarding future PIP modification are outlined below.

Currently Approved Paediatric Investigational Plan Summary (EMEA-001720-PIP01-14-M03)

Study number/completion date	Key design feature
Study 1 (EMERALD 1) By April 2021	Open-label study to evaluate dose, safety and tolerability of patiromer calcium in children from 6 years to less than 18 years of age with hyperkalaemia due to chronic kidney disease.
Study 2 By July 2025	Single-blind dose titration study to evaluate efficacy and safety of patiromer calcium in the treatment of hyperkalaemia in children from 2 years to less than 18 years of age with chronic kidney disease. At least 80 subjects evaluable for the primary endpoint.
Study 3 (EMAERALD 2) By December 2026	Open label, multiple dose, safety and pharmacodynamic study in children from birth to less than 6 years of age with hyperkalaemia. At least 12 subjects evaluable for the primary endpoint All subjects will be offered participation into a 52-week safety extension period.
Study 5 By June 2027	Extrapolation/interpolation population pharmacodynamic model to perform simulations to compare serum potassium response among paediatric and adult subjects

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

1.5. Additional Data exclusivity/Marketing protection

Not applicable.

1.6. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jayne Crowe

The application was received by the EMA on	9 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 March 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	13 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 August 2023
The PRAC Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	14 September 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	6 October 2023
The PRAC Rapporteur circulated the Assessment Report on the responses to the list of outstanding issues to all CHMP and PRAC members on	16 October 2023
The CHMP Rapporteur circulated the Assessment Report on the responses to the list of outstanding issues to all CHMP and PRAC members on	25 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP Rapporteur circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC	1 November 2023

members on	
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	9 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

While rare in the general population of healthy individuals with normal renal function, the prevalence of hyperkalemia 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).

The MAH originally proposed the following new therapeutic indication:

"Veltassa is indicated for the treatment of hyperkalaemia in adults and children of 6 years of age and older."

However, during the procedure, the indication was amended to only include paediatric subjects from 12 to 17 years:

"Veltassa is indicated for the treatment of hyperkalaemia in adults and adolescents aged 12 to 17 years."

2.1.2. Epidemiology and risk factors

CKD is by far the most common aetiology of hyperkalaemia in the paediatric population (> 80% of cases). The European Renal Association - European Dialysis and Transplantation Association registry (2009) reported an incidence of 100 to 200 patients per million (ppm) population of patients with end-stage renal disease that need any kind of renal replacement therapy (dialysis or transplantation). While CKD is a common adult disorder, the prevalence of CKD in the paediatric population is estimated to be much lower (Table 1). Prevalence estimates are typically < 100 per million of the population ≤ 16 years of age. Surveys from five European countries reported an annual incidence of CKD from 5.7 – 12.1 per million of the age-related population and a prevalence from 56 – 75 per million of the age-related population.

Table 1. Prevalence of Chronic Kidney Disease in Children

Country	**Belgium**	**Spain**	**France**	**Italy**	**Sweden**
Study Period	2001 – 2005	2007 – 2008	1975 – 1990	1990 – 2000	1986 – 1994
Age Range (years)	0 – 19	0 – 17	0 – 15	0 – 19	0.5 – 15
Prevalence[a]	56	71	66	75	59
Per million of the age-related population					

Estimating the total number of paediatric CKD patients with hyperkalaemia is challenging as there are no good current estimates on the number of paediatric CKD patients in the EU.

In children with CKD, the prevalence estimate of hyperkalaemia has been reported as stated in Table 2. The data were obtained by chart review of 366 patients at a single large paediatric nephrology centre in Canada. The overall prevalence of hyperkalaemia in this study of paediatric CKD patients was 1.6%. While the high cutoff for serum potassium as an inclusion criterion in this study may lead to an underestimation of the prevalence of hyperkalaemia in CKD paediatric patients, the general frequency of hyperkalaemia by stage of CKD is similar to the observed prevalence in adults.

Table 2. Prevalence of Hyperkalaemia in Children with Chronic Kidney Disease

KDOQI Stage	**CKD 1**	**CKD 2**	**CKD 3**	**CKD 4 – CKD 5**
GFR range ($mL/min/1.73m^2$)	> 90	60 – 90	30 – < 60	15 – < 30 (CKD 4) < 15 (CKD 5)
Number of patients	207	106	38	15
Percent of all CKD patients by severity	56.6	29.0	10.4	4.1
Percent with hyperkalaemia	0.5	0.9	5.3	18.2

CKD = chronic kidney disease; GFR = glomerular filtration rate. Source: {Wong, 2006 #95}

An analysis of the serum potassium data from the ongoing Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study provides additional estimates of the frequency of hyperkalaemia in the paediatric CKD population. Table 3 shows a summary of the distribution of 3,484 serum potassium measurements from this study in 669 CKD patients who had assessments of their kidney function including those on and not on dialysis. Similar to adults, the frequency and severity of hyperkalaemia in paediatric CKD patients increases with worsening renal function and is highest in those with CKD Stage 4, 5 and those on dialysis.

Table 3. Frequency and Severity of Hyperkalaemia by Chronic Kidney Disease Stage in Paediatric Patients[a]

CKD Stage	Number of Serum Potassium Measurements	< 4.8 mEq/L (%)	4.8 – 5.4 mEq/L (%)	5.5 – 5.9 mEq/L (%)	≥ 6 mEq/L (%)
CKD 2	173	87.8	11.6	0	0.6
CKD 3a	281	74.0	21.0	4.6	0.4
CKD 3b	767	71.2	25.7	2.3	0.8
CKD 4	1,561	66.8	26.8	5.6	0.8
CKD 5	282	68.4	22.0	7.5	2.1
PD	213	66.7	23.0	7.5	2.8
HD	207	49.8	33.8	11.1	5.3
CKD = chronic kidney disease, PD = peritoneal dialysis; HD = hemodialysis. Subjects included in the observations included paediatric CKD patients ages 5.5 to 21.3 years old					

These calculated prevalence estimates of hyperkalaemia in paediatric CKD patients may underrepresent the actual prevalence of CKD in the paediatric population. If dialysis patients are included, where the prevalence of hyperkalaemia is expected to be higher than non-dialysis CKD patients, the number of patients available for study would be higher.

Similar to adults, hyperkalaemia can also occur in paediatric patients in a hospitalised setting from a number of acute causes including acute renal failure, sepsis and metabolic acidosis, tumour lysis syndrome in the setting of leukaemia, massive transfusions and crush injuries from trauma.

As is stated in the product information, the onset of action of Veltassa occurs 4 – 7 hours after administration and thus it should not replace emergency treatment for life threatening hyperkalaemia.

2.1.3. Clinical presentation, diagnosis

Hyperkalaemia is associated with severe cardiac and arrhythmic adverse events thus treatment is important in reducing the risk of secondary harm.

2.1.4. Management

Treatment can involve the reduction of potassium through dietary means, avoidance of medicines which further reduce potassium elimination, administration of substances aimed at promoting a shift of potassium from extracellular to intracellular spaces, sequestration and secondary elimination of potassium through the use if binding agents and ultimately the removal of potassium through various renal replacement therapies, such as dialysis.

2.2. About the product

Veltassa contains the active substance, patiromer sorbitex calcium which belongs to the pharmacologic class of Potassium Binders. The active moiety is the polymer anion, 'patiromer anion', and is a non-absorbed, cation-exchange polymer that binds potassium in the lumen of the gastrointestinal (GI) tract and increases faecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels.

2.3. Type of application and aspects on development

No scientific advice with regard to the proposed indication has been requested. For aspects related to the paediatric development, see section 1.3.

2.4. Quality aspects

2.4.1. Introduction

The finished product introduced by this line extension is a powder for oral suspension containing 1.0 g of patiromer, as sorbitex calcium complex. This new strength is to be added to the three already marketed strengths of the same dosage form containing 8.4 g, 16.8, and 25.2 g of patiromer.

The other ingredient of the powder is: xanthan gum.

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

This line extension application has been grouped with a type II variation to request the extension of the approved therapeutic indication to the paediatric population: patients aged 12 to less than 18 years old, to the dosing of the paediatric population.

2.4.2. Active Substance

No change has been declared by the applicant on any section of the dossier supporting the active substance.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a powder for oral suspension containing 1.0 g of patiromer (as patiromer sorbitex calcium). The active substance, patiromer sorbitex calcium, is a polymer manufactured as an amorphous, free-flowing powder that is composed of individual spherical beads of approximately 100 micrometer diameter. The qualitative composition of the 1.0 g strength is identical to that of the authorised strengths. The weight proportions of the active substance and of the only excipient xanthan gum are the same across all the strengths.

As in the already authorised strengths, xanthan gum is the only excipient of the formulation. It is used as suspending agent. It is a well-known pharmaceutical ingredient, and its quality is compliant with Ph. Eur. standards. Following a request from the CHMP, the applicant provided a comprehensive discussion on the safety of the use of xanthan gum in the paediatric population. Based on the maximum daily doses of patiromer in the indicated age groups, the maximum quantity of xanthan gum administered with the finished product is well below the average level of exposure to this ingredient from food consumption. Therefore, it is concluded that the quantity of xanthan gum in the finished product is safe for use in the paediatric population.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development was to develop a product strength that allows dosing for the proposed paediatric population. As indicated above, this line extension application has been submitted together with a type II variation to request the extension of the approved therapeutic indication to patients aged 12 to less than 18 years old. This new 1.0 g strength will mostly be used as a starting dose for titration while providing flexibility to patients who will not be using adults' presentations as a maintenance dose. The starting dose in children (4 g patiromer) implies to use 4 sachets and the maximum number of sachets to be administered before switching to the adult presentation (8.4 g) is 7.

The quality target product profile (QTPP), similarly to the authorised adults' presentations, 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.

Therefore, the pharmaceutical development of Veltassa 1.0 g mainly focused on the evaluation of the volume of water necessary to adequately suspend this lower strength of the finished product. The suspendability of the powder (as 2 g of finished product corresponding to 1 g of patiromer) was evaluated in different volumes of water after 3 minutes from suspension. The pourability of the suspension was performed by measuring the weight of the residual polymer remaining in the original container following pouring over 8 seconds into a secondary container. These experimental conditions are in line with those used for the determination of the required volume of water for suspending the authorised higher strengths. The results of this study demonstrated that Veltassa 1.0 g is adequately suspended in 5 to 20 mL water. Significant sedimentation was observed for volumes of above 10 mL after 3 minutes from dispersion, suggesting that the suspension should preferably be taken immediately after preparation. Nonetheless, as for the authorised product strengths, it is agreed that the following instructions for administration included in the SmPC are supported: "The mixture should be taken within 1 hour of initial suspension. If powder remains in the glass after drinking, more water should be added, and the suspension stirred and taken immediately. This may be repeated as needed to ensure the entire dose is administered."

As indicated in the SmPC, the following liquids or soft foods can be used instead of water to prepare the mixture: apple juice, cranberry juice, pineapple juice, orange juice, grape juice, pear juice, apricot nectar, peach nectar, yoghurt, milk, thickener (for example: cornstarch), apple sauce, vanilla, and chocolate pudding.

Compatibility studies with these liquids and soft foods have not been repeated as part of the development of the 1.0 g strength. However, the compatibility study previously performed for the authorised strengths covered a range of concentrations of the suspension applicable also to the paediatric dose and support their

use also for the 1.0 g strength. The complete instructions for administration are described in section 4.2 of the SmPC.

The palatability of the formulation was studied in the context of the EMERALD trial. No subject withdrew from the study for palatability reasons. No issues with palatability in the paediatric population are envisaged.

Studies to evaluate the compatibility of the formulation with a variety of nasogastric and gastrostomy tubes have been performed. The aspects evaluated in these studies were syringeability of the finished product suspension, dose delivery and compatibility of the suspension with polyurethane, silicone, and PVC feeding tubes, in line with the recommendations provided in the EMA Q&A on the administration of oral immediate release medicinal products through enteral feeding tubes.

The results of these studies support the instructions for administration *via* nasogastric tube or percutaneous endoscopic gastrostomy tube included in section 6.6. of the SmPC.

The primary packaging for the 1.0 g strength is a sachet made of 5-layers: PE, aluminium foil, PE, polyester, and paper. The sachets are identical to those already in use for the authorised strengths, the only difference is the sachet dimensions, being 60 × 70 mm for the 1.0 g strength. The product contact surface (PE layer) complies with the Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come in contact with food and all its amendments and meets the requirements for the materials used for the manufacture of containers in Ph. Eur. 3.1.3 "Polyolefins" and Ph. Eur. "Polyethylene without additives for containers for parental preparations and for ophthalmic preparations". The choice of the container closure has been validated by stability data on the 1.0 g strength and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process for the 1.0 g strength is essentially the same as that used for the authorised strengths at the currently registered manufacturing, quality control and batch release sites. Since this strength is intended for the use in the paediatric population for which market demand is limited, the downscaling of the commercial batch size is accepted.

Process validation for the manufacture of the 1.0 g strength has not yet been performed. It will be conducted on three consecutive batches prior to placing the product on the market in line with the process validation scheme provided. This is accepted.

2.4.3.3. Product specification

The tests of the release and shelf-life specifications for the new 1.0 g strength are identical to the authorised adults' strengths. The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), suspendability of the finished product (visual), identification (FTIR, presence of calcium), patiromer anion content (gravimetry), uniformity of dosage units by weight variation (Ph. Eur.), total potassium exchange capacity (IC), calcium content (IC), loss on drying (gravimetry), fluoride (F-ISE), extractable impurities, individual unspecified and total impurities (all by HPLC-UV), total aerobic microbial count (Ph. Eur.), total combined yeasts and molds count (Ph. Eur.) and specified organisms -*E. coli*- (Ph. Eur.).

The product specifications cover appropriate parameters for this dosage form.

The specification limit for fluoride has been re-assessed within this line extension considering the extension of the indication to the paediatric population. With regards to safety aspects, the tolerable upper limits of fluoride intake from all sources have been established as 0.12 mg/kg body weight per day or 5 and 7 mg/day for children and adolescents aged 9-14 and 15 years and older, respectively (reference EFSA Scientific Opinion on Dietary Reference Values for fluoride; EFSA Journal 2013; 11(8):3332). The fluoride formed during shelf-life is in the form of calcium fluoride. Literature data have been provided which show that the absorption of calcium fluoride is about 30%. Considering the low absorption of calcium fluoride, the shelf-life limit allows the administration of a maximum amount of fluoride per day with the maximum dose of 25.2 g of patiromer which is below the tolerable upper limit intake of fluoride in the age groups of 12-17 years.

No nitrosamine risk assessment has been provided within this line extension application since the formulation and manufacturing process are identical to the authorised strengths.

The analytical methods used are generally the same as for the authorised strengths. They were adequately described and appropriately validated in accordance with the ICH guidelines. Solely the analytical method for suspendability testing was amended for the analysis of the 1.0 g strength. A detailed description of this method and its validation has been presented within this line extension application. No new information regarding reference standards has been presented.

Batch analysis results are provided for three commercial scale batches of Veltassa 1.0 g manufactured by the proposed finished product manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (2-8ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. In addition, an in-use stability study was also conducted on one commercial scale batch. The batch was stored for 6 months at 25 ºC / 60% RH after being stored for 30 months at 5 ºC, and for up to 3 months at 25 ºC / 60% RH after being stored for 33 months at 5 ºC.

The batches of Veltassa 1.0 g are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, suspendability/redispersibility, patiromer anion content, total potassium exchange capacity, loss on drying, fluoride, extractable impurities, individual and total unspecified impurities, total aerobic microbial counts, total combined yeast and moulds count, *E.coli* (*E. coli* not tested in one of the batches). The analytical methods used were the same as for release and were stability indicating.

The long-term and accelerated stability data available for the 1.0 g strength show that all the batches complied with the shelf-life specification at all the tested timepoints. No specific trends can be identified.

The available accelerated and long-term stability data support the proposed shelf-life of 36 months when refrigerated at 2°C – 8°C. The available in-use stability data support the proposed labelling that allows the finished product to be stored in the sachet at room temperature (below 25°C) within 6 months of being taken out of the refrigerator. This in-use period will be within the total shelf-life of 36 months.

2.4.3.5. Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

With this line extension application, a 1.0 g strength is being introduced to allow dosing of Veltassa in paediatric patients. The development of this new strength was based on the approved strengths.

Information on development, manufacture and control of finished product has been presented in a satisfactory manner. The manufacturing process of Veltassa 1.0 g is essentially the same as that used for the currently authorised strengths.

In terms of formulation development, an additional suspendability/pourability study was performed to investigate the adequate volume of water (or aqueous solution) to suspend Veltassa 1.0 g. A new compatibility study between the formulation and a variety of nasogastric and gastrostomy tubes intended for administration of the finished product was also conducted.

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.

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

A comprehensive non-clinical program was conducted as part of the initial marketing authorisation in adults, indicating no safety signal or toxicity. Patiromer has been shown in PK studies to be non-absorbable and no effects on growth or development of the paediatric population are expected. The paediatric GI tract anatomic and physiologic properties in children greater than 2 years of age up to adolescence are essentially similar to adult subjects. The applicant is of the opinion that the non-clinical toxicity studies conducted to date, together with the results of the clinical studies conducted in adults support the initiation of studies in paediatric subjects, thus no additional non-clinical studies, including juvenile toxicity studies, are necessary to support the administration of patiromer in the paediatric population in clinical trials. This is considered acceptable to the CHMP.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH 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.

- **Overview of clinical studies**

The applicant has conducted one clinical trial, which is further supported by an extrapolation study:

A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 6 to <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD).

The trial was initially intended to recruit patients from 2 to 18 years, but due to recruitment difficulties and associated delays, the PDCO agreed that the cohort from 2 to 6 years could be moved from this study to another study also included in the PIP. This could facilitate the assessment of data already generated in the Emerald study.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

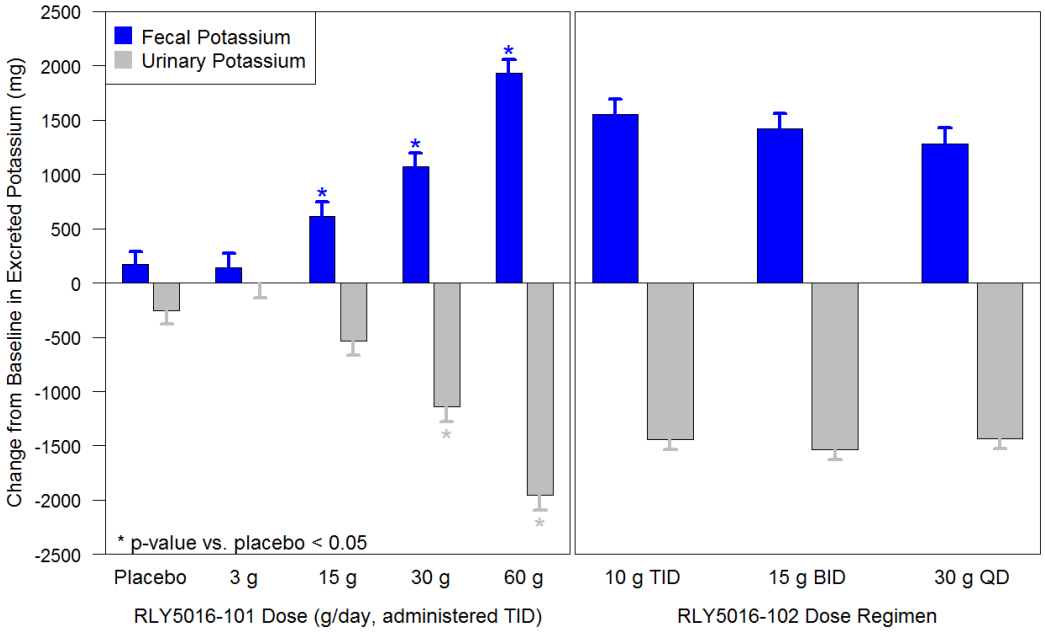
Patiromer belongs to the pharmacologic class of potassium binders. The active moiety, the polymer anion, is a non-absorbed, cation-exchange polymer that binds potassium predominantly in the lumen of the colon where potassium is the most abundant cation, due to active secretion and where the residence time of the polymer is the longest. This increases faecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in the hyperkalemic patient. As distribution of the polymer is restricted to the GI tract, patiromer is expected to be excreted after approximately 24 – 48 hours based on average GI transit time.

It is expected that the oral suspension will act in a similar way in paediatric subjects over the age of 2 years old as in adults due to similarities in the anatomy and physiology of the GI tract. The binding of potassium in the GI tract using cation exchange is similar to other approved, non-absorbable, oral potassium binders which use exchange with sodium (sodium polystyrene sulfonate) or calcium (calcium polystyrene sulfonate) as a mechanism for potassium binding in the GI tract. Considering this

Data from the adult clinical development programme inform about the pharmacological rationale for further testing in the paediatric population. In two Phase 1 clinical studies involving 45 healthy subjects (RLY5016-101 and RLY5016-102), RLY5016 for oral suspension was shown to increase faecal potassium excretion. In study RLY5016-101, statistically significant dose-dependent increases in mean faecal potassium excretion from baseline occurred in the RLY5016 for oral suspension groups compared with the placebo group. There was a corresponding dose dependent decrease in urinary potassium excretion. Since this study only included heathy volunteers, as expected, no dose related trend was apparent in serum potassium. Similar increases in

faecal potassium and decreases in urinary potassium were seen in study RLY5016-102 (Figure 1) when the total daily dose was administered once a day or divided into twice or three times a day dosing. The decrease in urinary potassium excretion is a normal compensatory mechanism that maintains serum potassium in healthy volunteers following increased gastrointestinal loss of potassium. In a Phase 2a proof-of-concept study conducted in six haemodialysis patients with hyperkalaemia 12.6 g/day patiromer for 7 days resulted in increased faecal potassium excretion and decreases in serum potassium from baseline (RLY5016-201). Results from these three clinical pharmacology studies confirm the mechanism of action of RLY5016 for oral suspension.

Figure 1. Fecal and Urinary Potassium Excretion in Studies RLY5016-101 and RLY5016-102



Left Panel (Study RLY5016-101): Dose response evaluated using different total daily doses. **Right Panel (Study RLY5016-102)**: Different dose regimens evaluated using the same total daily dose.

Note: In Study RLY5016-101, RLY5016 doses of 3 g, 15 g, 30 g and 60 g are equivalent to 2.5 g, 12.6 g, 25.2 g and 50.4 g patiromer, respectively. In Study RLY5016-102, RLY5016 doses of 10 g, 15 g and 30 g are equivalent to 8.4 g, 12.6 g and 25.2 g patiromer, respectively.

2.6.2.2. Pharmacodynamics

Population Pharmacodynamic Modelling and Simulation of Patiromer to Support Paediatric Extrapolation in Patients with Hyperkalaemia

The objective of this analysis was to confirm the patiromer starting dose required for paediatric subjects to yield serum potassium responses comparable to those observed in adults at the established efficacious dose of 8.4 g/day. Data were pooled from one paediatric phase 2 study (RLY5016-206p), one adult phase 2 study (RLY5016-205) and one adult phase 3 study (RLY5016-301). In total, 571 subjects and 9999 serum potassium observations were included in the analysis. Paediatric data contributed 337 (3.4%) observations from 23 paediatric subjects (14 patients aged 12-<18 years and 9 patients aged 6-<12 years).

An indirect response model was selected to describe the potassium concentration-time course driven by patiromer dose. This model assumed that response to patiromer occurred as potassium moved from the

precursor to the central compartment, described by a first-order rate of transfer from the precursor compartment (K_{tol}). Drug effect was assumed to inhibit K_{tol} *via* a maximum effect (E_{max}) model. The precursor and central compartments were assumed to start at steady baselines.

While an E_{max} model was used, it became clear that estimate for D50 was continually going to a very small number. Eventually, D50 was fixed to 0.1 g/day to mimic an on-off type drug effect where any dose resulted in a maximum effect. This approach was justifiable given the exploratory plots showed all subjects appeared to have a maximal effect, regardless of dose level.

Final model

The final model included the following covariate effects estimated on both BASE and I_{max} parameters: RAAS inhibitor concomitant medication (yes versus no), heart failure (yes versus no), myocardial infarction (yes versus no), type 2 diabetes (yes versus no), sex, (male versus female), age and eGFR. Body weight was not included due to its high correlation with age.

Parameter estimates of the final model are presented in Table 4 and Table 5. VPCs for the final model are presented in Figure 2.

Table 4. PD Final Model: Summary of population PD fixed effects parameter estimates

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

Parameters estimated in the logit-domain were back-transformed for clarity
Abbreviations: CI = confidence intervals; EGFR: estimated glomerular filtration rate; RAASI: renin-angiotensin-aldosterone-system inhibitor; SE: standard error
Confidence intervals = estimate ± 1.96 · SE

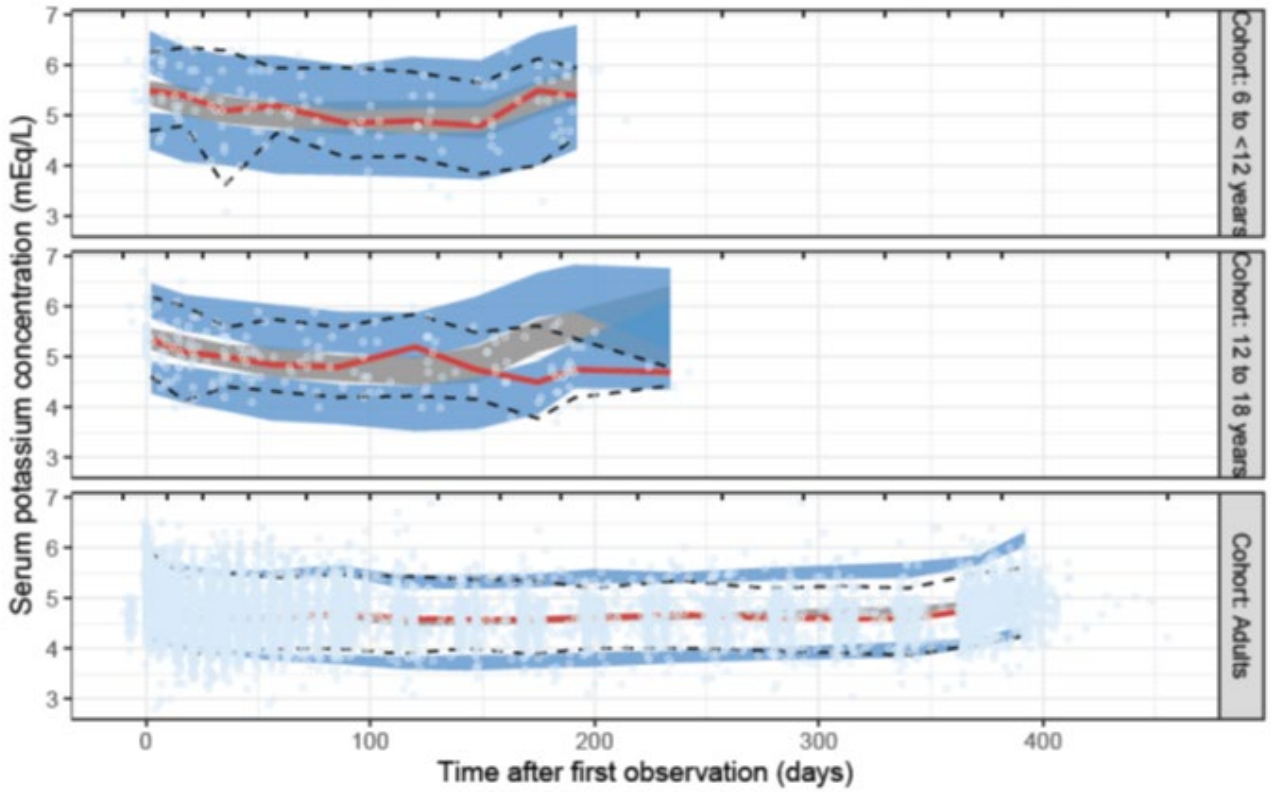
Table 5. PD Final Model: Summary of population PD random effects parameter estimates

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

Abbreviations: CI = confidence intervals; Corr: correlation coefficient; CV: coefficient of variation; SD: standard deviation; RUV: residual unexplained variability
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100

Figure 2. PD Final Model: Visual predictive check (VPC) of potassium concentration over time; stratified by cohort

The lines represent the median (solid) or 5th / 95th (dashed) percentiles of the observed data. The shaded areas represent 95% prediction intervals for median (grey) or 5th / 95th percentiles for data simulated under the model. The points are observed potassium concentrations. Day 0 indicates the day of first dose given.



The impact of individual covariate effects was assessed *via* forest plots for BASE and Imax (Figure 3 and Figure 4).

Figure 3. PD Final Model: Covariate effect forest plot: baseline potassium (BASE)

Covariates in the final population PD model were varied one at a time from the reference subject, i.e., a 66-year-old female subject with an eGFR of 30.43 mL/min/1.73m^2 and without RAAS inhibitor concomitant medication, heart failure, myocardial infarction or type 2 diabetes. These were used to simulate baseline potassium in N=500 parameter sets from the covariance matrix of the fixed effect estimate. The symbols indicate the median and the whiskers show the 95% prediction interval for the simulated baseline potassium.

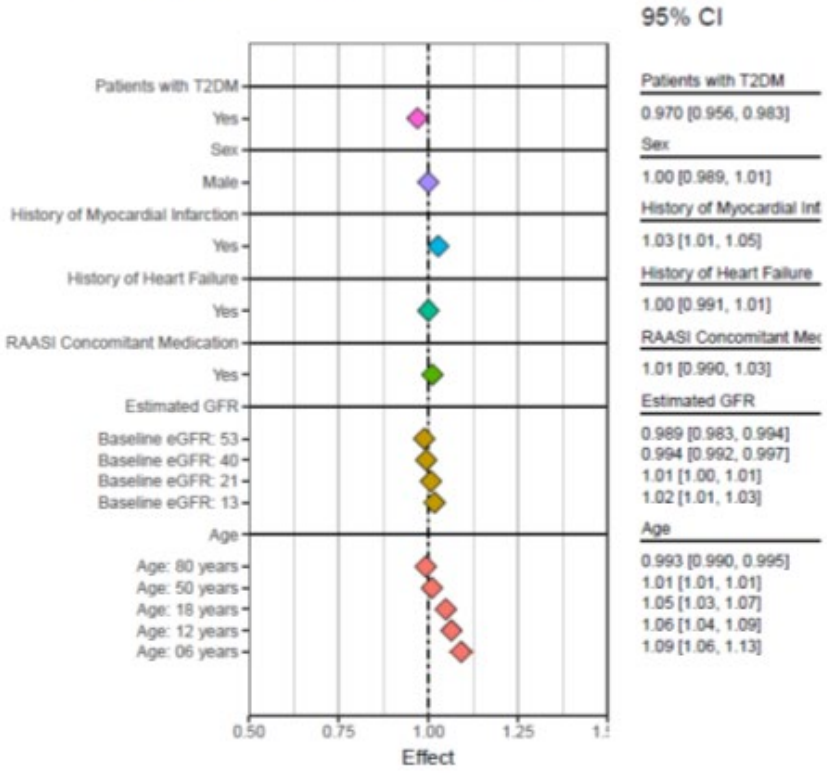
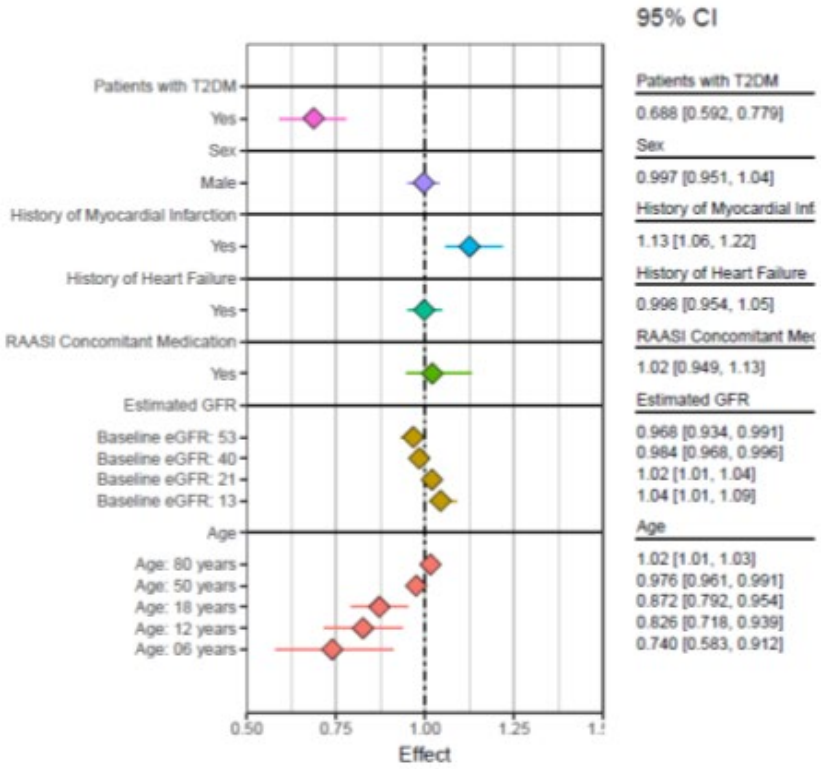


Figure 4. PD Final Model: Covariate effect forest plot: maximum inhibition (Imax)

Covariates in the final population PD model were varied one at a time from the reference subject, i.e., a 66-year-old female subject with an eGFR of 30.43 mL/min/1.73m^2 and without RAAS inhibitor concomitant medication, heart failure, myocardial infarction or type 2 diabetes. These were used to simulate Imax in N=500 parameter sets from the covariance matrix of the fixed effect estimate. The symbols indicate the median and the whiskers show the 95% prediction interval for the simulated Imax.



Additional population simulations were performed to examine age effects on serum potassium response. Individual maximum change from baseline for each age group and individual mean change from baseline at one year were plotted to explore the trends across these groups. In general, the distributions of change from baseline were similar across age groups, except for a trend of increasing median change from baseline with increasing age. To further examine the paediatric response over a range of doses, population simulations were also performed for 6 to < 12-year-old subjects at doses of 4 g/day, 4.2 g/day, 8.4 g/day, 12.6 g/day, and 16.8 g/day with 1000 subjects simulated at each dose level. The response was comparable across this range of dose levels.

2.6.3. Discussion on clinical pharmacology

Population PD analysis was conducted to support dosing and efficacy of patiromer in the paediatric population. The potassium concentration time-course was described by an indirect response model driven by patiromer dose. Covariate effects included in the final model were concomitant RAAS inhibitor medication, heart failure, myocardial infarction, type 2 diabetes, sex, age and eGFR. However, none of these covariates were considered to have a clinically meaningful impact on serum potassium response to patiromer dosing.

Final model parameters were estimated with reasonable precision. Shrinkage was low for IIV-BASE and IIV-RUV parameters but reasonably high for IIV-I_{max} (36%). However, empirical Bayes estimates were not used for model selection and Monte Carlo simulations were conducted. Therefore, the shrinkage of IIV-I_{max} is not a

major concern. The diagnostic plots and VPCs suggested that the final model described the adult and paediatric data reasonably well, although there were limited data in paediatric subjects.

The dose required for 50% of the effect (D50) was fixed to 0.1 g/day to mimic an on-off type drug effect, where any dose resulted in a maximum effect. The applicant considers that this approach was justifiable given that the exploratory plots showed all subjects in the analysis population appeared to have a maximal effect, regardless of dose level. Section 4.2 of the SmPC states that proposed daily dose of patiromer may be adjusted based on serum potassium level. This is accepted. According to the applicant, the population simulations indicated that a starting dose of 4.2 g/day for paediatric subjects is likely to yield patiromer effects that are comparable to those observed for the recommended 8.4 g/day starting dose in adult hyperkalaemia patients. Nevertheless, the simulation results suggest a lower response to patiromer in paediatric patients, particularly in 6-12, year-old patients. For further discussion, see clinical efficacy section.

Overall, given the limited difference in response across the range of dose levels, it is agreed that a 4.0 g/day patiromer dose is likely to yield an equivalent effect to 4.2 g/day.

2.6.4. Conclusions on clinical pharmacology

During the evaluation, the CHMP raised a number of other concerns, and these have been resolved by the applicant. The appropriateness of the PD model for describing the relationship between patiromer dose and potassium concentration is not pursued since even an updated model would likely not be able to support dose, dose frequency or efficacy in paediatric patients 6 - <12 years of age. However, given the restriction of the ultimately granted indication to patient of 12-17 years of age, this issue is not relevant (see section on clinical efficacy and safety).

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

The Phase 2 multiple dose study is the pivotal study for this application. It will be described below.

2.6.5.2. Main study

Title of study

In order to support the application, the applicant has included one clinical trial, which is further supported by an extrapolation study:

A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 6 to <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD)

Methods

- **Study Participants**

Inclusion criteria

1. Written assent (when applicable) and written informed consent by a legally authorised representative provided prior to participation in the study.
2. Age 2 to <18 years old.
3. Paediatric subjects with CKD and eGFR <90 ml/min/1.73 m^2 calculated using the Schwartz formula, including renal transplant subjects, based on local creatinine measurement at screening.
4. Two blood or serum potassium measurements of 5.1 to <6.5 mEq/l performed on separate days.
5. In the opinion of the investigator, the subject was expected to require treatment for hyperkalaemia for at least 6 months.
6. If taking any RAAS inhibitors, beta blockers, fludrocortisone, or diuretic medications, patient must be on a stable dose for at least 28 days prior to screening.
7. Females of childbearing potential must be non-lactating, have a negative pregnancy test at screening and must have used an effective form of contraception (e.g., abstinence, hormonal, chemical, physical barrier, etc.) for at least 1 month before patiromer administration. Subjects of childbearing potential must agree to continue using contraception throughout the study and for 1 month after the last dose of patiromer.

Exclusion Criteria

1. Subjects with pseudo-hyperkalaemia due to haemolysis or abnormally high numbers of platelets, leukocytes, or erythrocytes at screening.
2. Any subject with evidence of potential potassium-related ECG changes (i.e., changes consistent with hyper- or hypokalaemia) at screening.
3. Any of the following renal conditions: maintenance haemodialysis or peritoneal dialysis, renal artery stenosis, and acute kidney injury or a history of acute renal insufficiency in the past 3 months.
4. A history of or current diagnosis of a severe GI diagnosis or surgery that could affect GI transit of the drug (e.g., a severe swallowing disorder, uncorrected pyloric stenosis, intussusception, any other intestinal obstruction.
5. A history of or current diagnosis of a condition that in the opinion of the investigator increases the risk of aspiration of patiromer if given orally.
6. ALT, AST >3 times upper limit of normal at screening.
7. Active cancer, currently on cancer treatment or history of cancer in the past 2 years (except for non-melanoma skin cancer).
8. Heart or liver transplant recipient, or anticipated need for transplant during the study treatment period, including a scheduled kidney transplant recipient.
9. Chronic alcohol abuse or substance use disorder within 1 year of screening.

10. Subjects currently being treated with or having taken any one of the potassium-lowering medications (includes resins) in the 7 days prior to screening.

11. Use of medications with known effects on potassium levels if doses were not stable for at least 14 days prior to screening or if doses are anticipated to change during the 14-day PD/dose finding phase.

A total of 36 patients were initially intended to be recruited to the trial, 12 per each age cohort. However, due to recruitment difficulties, recruitment to the lowest age cohort of 1 to 6 years did not occur. This reduced the trial patient size to 24. In addition, the recruitment challenges meant that only 9 patients were ultimately recruited to the cohort from 6 to 12 years, and 14 patients were recruited to the older age cohort.

The applicant requested a modification to the PIP to take these difficulties into account, moving the lowest age cohort to a later study and introducing an extrapolation study to compensate for the loss of the three patients in the 6-12 years age group. This proposal was accepted by PDCO on the basis of the mechanism of action and the likelihood of similarity across the various age cohorts.

The inclusion and exclusion criteria are appropriate.

- **Treatments**

Up to 3 starting dose levels were to be evaluated in each age group. The initial dose evaluated was the lowest of the planned starting dose levels for each age group.

The planned starting dose levels of patiromer for each age cohort were:

- Age 12 to <18 years: 4.2 g/day, 8.4 g/day, and 16.8 g/day
- Age: 6 to <12 years: 2.0 g/day, 4.0 g/day, and 8.0 g/day

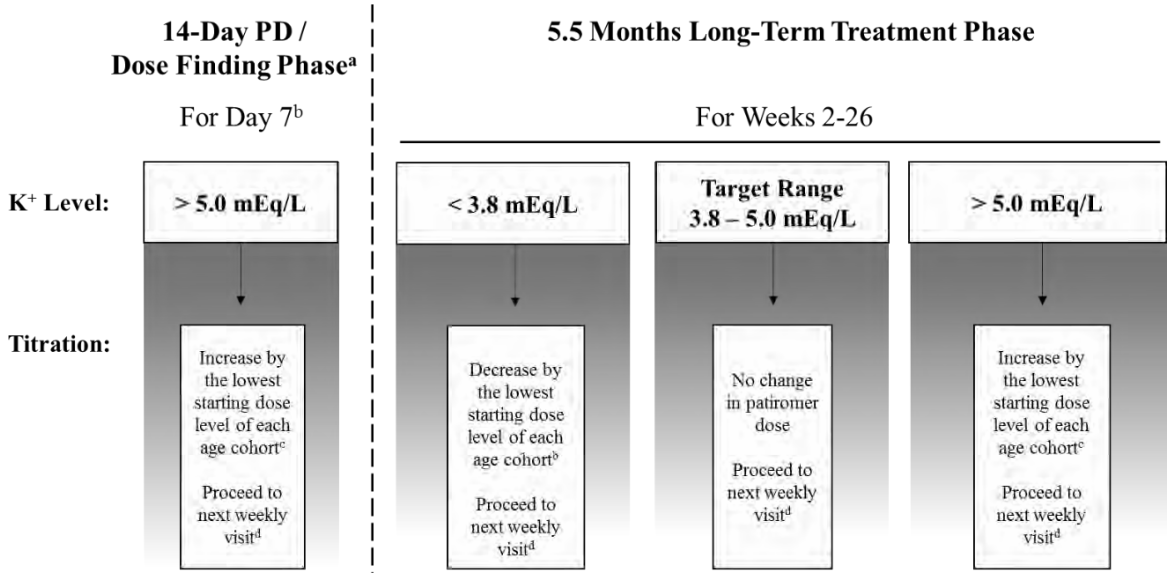
The starting doses of patiromer in each age cohort were selected based on the median weights for boys and girls within each of the age categories using standard growth data. The initial weight-based doses selected were guided by the starting dose in adults (8.4 g/day patiromer), a higher commonly used dose in adults (16.8 g/day) and a dose below the adult efficacy range (4.2 g/day patiromer) in the event children have a different response profile than in adults.

Patiromer dose titration was allowed during study visits to achieve and maintain potassium levels in the 3.8 to 5.0 mEq/l range. Titrations were to be based on potassium levels measured locally and per the protocol-specified algorithm.

Patiromer dose adjustments were planned to be made in increments or decrements that represent the lowest starting dose of patiromer for each age group. Specifically, the following dose adjustments were allowed:

- For participants aged 12 to <18 years: titrations up or down by 4.2 g/day
- For participants aged 6 to <12 years: titrations up or down by 2.0 g/day

Figure 5. Planned Patiromer Dose Titration Algorithm



a At Day 3, as a safety measure to ensure that subject exposure to hyperkalaemia was not prolonged, patiromer dose could be up-titrated only if the potassium level was ≥5.5 mEq/l and was greater than the most recent locally obtained screening potassium value. Note: At the discretion of the Investigator, the Day 3 visit was optional for participants whose last screening potassium was <5.5 mEq/l; for participants whose last screening potassium was ≥5.5 mEq/l, the Day 3 visit was to be mandatory.

b Down-titration of patiromer dose by the designated decrement for each age cohort or more was allowed for any potassium values <3.8 mEq/l to a minimum patiromer dose of 0.0 g/day. If patiromer dose required titration, then initiation of the titrated patiromer dose was to occur at the next planned administration.

c Dose titration was not required if the potassium decrease from the previous visit was ≥0.5 mEq/l.

d If patiromer dose required titration, then initiation of the titrated patiromer dose was to occur at the next planned administration. Participants were required to return for a mandatory safety visit within 7 days if the next scheduled study visit was >1 week after a dose increase had been initiated. Unscheduled visits were to occur during any phase of the study at the discretion of the Investigator. Refer to Section . .1 of the protocol for additional information and criteria for mandatory safety visits.

Note: PD=Pharmacodynamic.

Although it is accepted that the starting dose for patients 6 to <12 years ultimately turned out to be too low, the initial rationale for the choice of starting doses and dose adjustments was appropriate.

- **Objectives**

The primary objective of the trial was to assess change from baseline in serum potassium levels to Day 14 following administration of different doses of patiromer administered QD in children 6 to <18 years of age with CKD and hyperkalaemia. The secondary objective was to assess the safety and tolerability of patiromer in children 6 to <18 years of age with CKD and hyperkalaemia. The primary and secondary objectives are appropriate for the assessment of this type of medicine.

- **Outcomes/endpoints**

Primary efficacy endpoint: Change in serum potassium levels from baseline to Day 14.

Secondary efficacy endpoints:

– Proportion of participants with serum potassium levels in the range of 3.8 to 5.0 mEq/l at Day 14 (initial PD/dose finding phase).

– Proportion of participants with serum potassium levels in the range of 3.8 to 5.0 mEq/l by visit at any time through Month 6 (LT treatment phase).

The efficacy endpoints are in line with the objectives of the trial.

- **Sample size**

Sample size was selected to maximise information for selected starting doses while minimising exposure of children to ineffective starting doses. With a sample size of 12 participants in each age cohort at the identified efficacious and safe starting dose, and assuming a 100% probability of achieving potassium level within the normal range (3.8 to 5.0 mEq/l), the lower bound of the 95% exact CI for achieving this success rate was calculated to be 73%. The sample size chosen for the study is acceptable, although the lower bound of the CI for success appears on the lower end. The applicant had discussed this aspect with PDCO who accepted that the proposed extrapolation exercise could help support the assessment of efficacy in the paediatric population.

- **Randomisation and Blinding (masking)**

Not applicable as this was a non-randomised, single arm, open label trial.

- **Statistical methods**

For the primary endpoint, changes from baseline to Day 14 in serum potassium levels, was to be summarised using descriptive statistics. Baseline potassium was to be the last non-missing central serum potassium value prior to first dose of patiromer. Descriptive statistics included mean, SD, and 95% CIs. For the secondary endpoint, number and proportion of participants with central serum potassium levels in the range of 3.8 to 5.0 mEq/l at Day 14 (initial PD/dose finding phase) and proportion of participants with central serum potassium levels in the range of 3.8 to 5.0 mEq/l by visit through Month 6 (LT treatment phase) were planned to be presented. Proportions were to be provided along with the 95% CIs, obtained using exact (Clopper-Pearson) method. Central serum potassium and mean changes in serum potassium at each scheduled visit were presented graphically. Central and local laboratory potassium values from serum samples were included in listings. The statistical analyses are appropriate for the design of the study.

Results

- **Participant flow**

Of the 23 patients enrolled, 14 were recruited to Cohort 1 (12-18 years), while 9 were recruited to Cohort 2 (6-12 years). Patients were recruited sequentially to the two cohorts, with a minimum number of 12 as the target. However, there was scope to increase recruitment to a particular cohort, should adjustments to the starting dose be necessary, according to the DSMB.

- **Recruitment**

The first participant was screened on 31 May 2017 and last participant last visit was 30 April 2021.

- **Conduct of the study**

The most significant change to the study arose as a result of difficulties recruiting patients to the trial, both due to pandemic-related delays, and due to the anticipated low numbers of patients with the condition. This resulted in the design being changed to delete Cohort 3 (patients from 2 to 6 years) and study these patients in a different trial, already contained within the agreed PIP. This was agreed by PDCO.

The first participant was screened on 31 May 2017 and last participant last visit was 30 April 2021, which included the period during which the COVID-19 pandemic outbreak was ongoing. The trial was placed on hold from 4 April 2020 to 13 May 2020 and the sponsor implemented a regular review of the situation in all trial countries. The trial was reactivated on 25 June 2020. There was 1 new site activated. No protocol amendments and no changes to the SAP were implemented because of the pandemic and no other,

significant amendments were made to the protocol. The recruitment difficulties described by the applicant were noted by the CHMP.

The applicant requested a modification to their PIP (and a subsequent amendment to the study design) from the PDCO, stating the following:

"The applicant has completed Cohort 1 (aged 12 to <18 years) with 14 patients enrolled. Dosing in Cohort 2 (aged 6 to <12 years) is ongoing with nine patients enrolled as of 25 February 2021. Since Cohort 2 opened for screening in July 2019, enrolment has been very slow, slower than expected, despite extensive recruitment efforts. These recruitment difficulties for Cohort 2 (aged 6 to <12 years) were communicated by the applicant in the last Annual Report on Deferral Granted in the Paediatric Investigation Plan submitted to the EMA on 30 June 2020. It is anticipated that Cohort 2 (aged 6 to <12 years) would be completed by October 2021 (provided that 3 additional patients can be recruited by the end of March 2021, which is however highly unlikely. If the study can be terminated with the current 9 patients, the last subject's last study visit would be in April 2021. As a result of the recruitment difficulties in the age group 6 to 12 years (Cohort 2) and the sequential dosing implemented for this study (starting with the oldest Cohort 1, followed by Cohort 2 and only subsequently the youngest Cohort 3), dosing in Cohort 3 has not yet started. No subjects aged 2 to <6 years have been enrolled as of 25 February 2021. This delay in the enrolment of Cohort 3 (aged 2 to <6 years) will have a significant impact on the completion of Study 1. It is anticipated that Study 1 cannot be completed by 2022. Since Study 2 and Study 3 cannot be initiated until the completion of Study 1, this will result in subsequent delays in the completion of the PIP and the potential availability of patiromer to the paediatric population in the EU."

These difficulties were acknowledged by the PDCO, and the design and development plan altered as previously described.

- **Baseline data**

The mean (SD) age of participants in Cohort 1 (12 to <18 years of age) was 14.5 (1.99) years. The minimum age was 12 years (n=3 subjects), the maximum age was 17 years (n=3 subjects), the median age was 14.5 years.

The mean (SD) age of participants in Cohort 2 (6 to <12 years of age) was 8.0 (2.00) years. The minimum age was 6 years (n=3 subjects), the maximum age was 11 years (n=1 subject), the median age was 7.0 years.

All of the study participants were white. Most of the study participants were male, 60.9% (14/23 subjects) versus 39.1% (9/23 subjects) female. In Cohort 1, most of the participants were male (21.4% female, 78.6% male). In Cohort 2, most of the participants were female (66.7% female and 33.3% male). Mean (SD) body weight at baselines was 50.74 (12.308) kg (Cohort 1) and 24.40 (6.901) kg (Cohort 2). In Cohort 1, mean (SD) body mass index was 19.10 (2.983) kg/m^2. In Cohort 2, mean (SD) body mass index was 15.78 (2.022) kg/m^2. Both cohorts were similar with regards to their baseline potassium levels. Overall mean (SD) levels were 5.56 (0.359) mEq/l (Cohort 1: 5.54 (0.323) mEq/l; Cohort 2: 5.59 (0.439) mEq/l).

The baseline characteristics are as would be expected in this condition, although the number of participants is too small for detailed comment.

- **Numbers analysed**

The efficacy population includes all subjects who have taken at least 1 dose of patiromer. As the safety population and efficacy population are the same, all analyses are displayed with 1 population, i.e., safety population. The number of participants analysed in the study was 23.

- **Outcomes and estimation**

Primary efficacy endpoint

– Change in serum potassium levels from baseline to Day 14.

• Secondary efficacy endpoints

– Proportion of participants with serum potassium levels in the range of 3.8 to 5.0 mEq/l at Day 14 (initial PD/dose finding phase).

– Proportion of participants with serum potassium levels in the range of 3.8 to 5.0 mEq/l by visit at any time through Month 6 (LT treatment phase).

- **Ancillary analyses**

The population PD extrapolation study was described earlier.

- **Summary of main efficacy results**

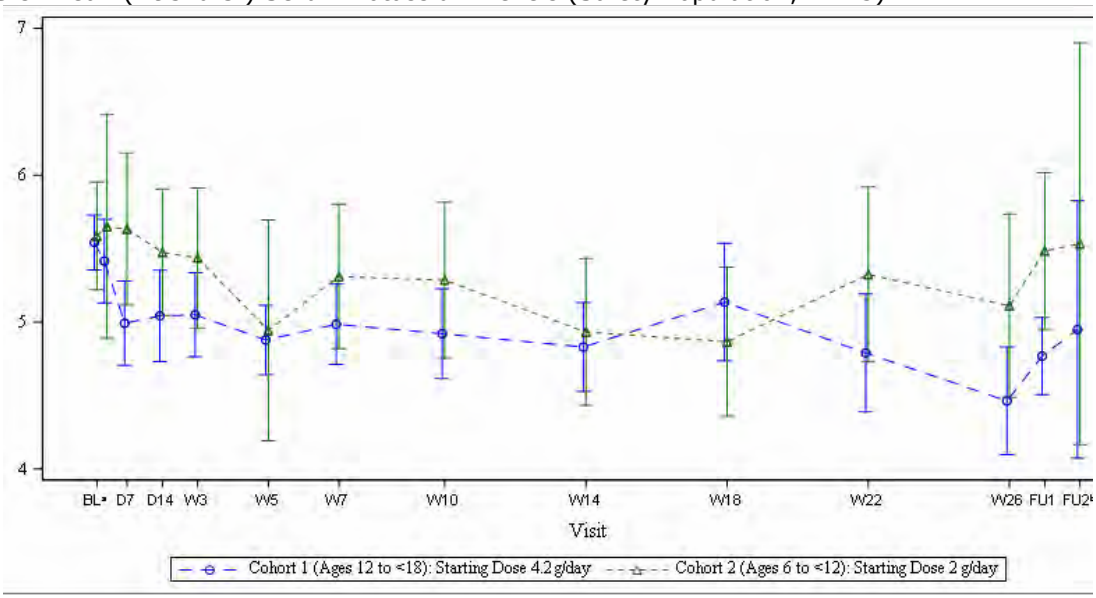
Primary outcome analysis

The primary efficacy analysis included the change in serum potassium levels from baseline to Day 14.

At baseline, the mean (SD) serum potassium values were 5.54 (0.323) mEq/l in Cohort 1 and 5.59 (0.439) mEq/l in Cohort 2. By Day 14, potassium levels decreased in both cohorts; mean (SD) potassium change from baseline was -0.50 (0.542) mEq/l in Cohort 1 and -0.14 (0.553) mEq/l in Cohort 2. At Week 3, mean (SD) potassium change from baseline was -0.49 (0.514) mEq/l in Cohort 1 and -0.11 (0.157) mEq/l in Cohort 2. At Week 26, mean (SD) potassium change from baseline was -1.08 (0.736) mEq/l in Cohort 1 and -0.50 (1.020) mEq/l in Cohort 2.

Of note, 1 subject in Cohort 2 did not have reportable central laboratory serum potassium measurements on Days 1 and 3. Hence, the baseline potassium was missing and not included in the analysis. A sensitivity post-hoc analysis was performed by imputing the serum potassium on Day 7 as the baseline potassium. There were similar changes seen in both male and female participants, although the participant numbers are too small for a robust conclusion to be drawn.

Figure 6. Mean (±95% CI) Serum Potassium Levels (Safety Population, N=23)



Notes: Baseline value was the last non-missing central laboratory value collected before the date and time of first dose of patiromer.
Follow-up 2 was an optional site visit and could be a phone call.
Serum potassium data on or after the date of initiation of dialysis were excluded. BL=Baseline;
CI=Confidence interval; D=Day; FU=Follow-up; W=Week.

Table 6. Central Laboratory Serum Potassium (mEq/l) Over Time and Change from Baseline (Safety Population, N=23)

Visit	Age Group				All Cohorts (N=23)	
	Cohort 1 (Ages 12 to <18): Starting Dose 4.2 g/day (N=14)		Cohort 2 (Ages 6 to <12): Starting Dose 2 g/day (N=9)			
	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline
Baseline[1]						
n	14		8		22	
Mean (SD)	5.54 (0.323)		5.59 (0.439)		5.56 (0.359)	
SE	0.086		0.155		0.077	
95% CI	(5.36, 5.73)		(5.22, 5.95)		(5.40, 5.72)	
Median	5.45		5.55		5.50	
Q1, Q3	5.30, 5.60		5.35, 6.00		5.30, 6.00	
Min, max	5.1, 6.2		4.8, 6.1		4.8, 6.2	
Day 14						
n	14	14	8	7	22	21
Mean (SD)	5.04 (0.539)	-0.50 (0.542)	5.48 (0.515)	-0.14 (0.553)	5.20 (0.560)	-0.38 (0.559)
SE	0.144	0.145	0.182	0.209	0.119	0.122
95% CI	(4.73, 5.35)	(-0.81, -0.19)	(5.04, 5.91)	(-0.65, 0.37)	(4.95, 5.45)	(-0.64, -0.13)
Median	5.05	-0.60	5.30	-0.20	5.20	-0.30
Q1, Q3	4.60, 5.40	-0.90, 0.10	5.15, 5.70	-0.80, 0.40	4.80, 5.40	-0.80, 0.10
Min, max	4.1, 6.1	-1.3, 0.4	5.0, 6.5	-0.9, 0.5	4.1, 6.5	-1.3, 0.5

Visit	Age Group				All Cohorts (N=23)	
	Cohort 1 (Ages 12 to <18): Starting Dose 4.2 g/day (N=14)		Cohort 2 (Ages 6 to <12): Starting Dose 2 g/day (N=9)			
	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline
Week 3						
n	14	14	8	7	22	21
Mean (SD)	5.05 (0.496)	-0.49 (0.514)	5.44 (0.571)	-0.11 (0.157)	5.19 (0.545)	-0.37 (0.461)
SE	0.132	0.137	0.202	0.059	0.116	0.101
95% CI	(4.76, 5.34)	(-0.79, -0.20)	(4.96, 5.91)	(-0.26, 0.03)	(4.95, 5.43)	(-0.58, -0.16)
Median	5.05	-0.50	5.40	-0.10	5.15	-0.30
Q1, Q3	4.80, 5.30	-0.90, -0.30	5.00, 5.90	-0.20, -0.10	4.90, 5.60	-0.70, -0.10
Min, max	4.2, 5.8	-1.2, 0.5	4.6, 6.3	-0.3, 0.2	4.2, 6.3	-1.2, 0.5
Week 26						
n	11	11	9	8	20	19
Mean (SD)	4.46 (0.546)	-1.08 (0.736)	5.11 (0.812)	-0.50 (1.020)	4.76 (0.737)	-0.84 (0.890)
SE	0.165	0.222	0.271	0.361	0.165	0.204
95% CI	(4.10, 4.83)	(-1.58, -0.59)	(4.49, 5.73)	(-1.35, 0.35)	(4.41, 5.10)	(-1.27, -0.41)
Median	4.30	-1.00	5.30	-0.30	4.75	-0.60
Q1, Q3	4.10, 4.80	-1.80, -0.60	4.90, 5.70	-0.75, 0.15	4.25, 5.30	-1.70, -0.20
Min, max	3.7, 5.7	-1.9, 0.3	3.3, 6.0	-2.7, 0.5	3.3, 6.0	-2.7, 0.5

1 Baseline value is the last non-missing central laboratory value collected before the date and time of first dose of patiromer.
Notes: CI=Confidence interval; N=Subjects in a cohort; n=Subjects with observation; Q1=25th percentile; Q3=75th percentile; SD=Standard deviation; SE=Standard error.

The results of the primary efficacy analysis show a significant decrease in serum potassium levels in participants in Cohort 1 and all analysis points. The results from cohort 2 are less clear. While there is a demonstrable decrease from baseline at Day 14, the magnitude of this decrease is significantly smaller than that seen in older patients. The decrease from baseline does increase in both cohorts over time; however, the decrease in younger patients remains smaller than that seen in older children.

Secondary efficacy analyses

The secondary efficacy endpoints were to assess the proportion of subjects with serum potassium levels in the range of 3.8 to 5.0 mEq/l at Day 14 (initial PD/dose finding phase) and the proportion of subjects with serum potassium levels in the range of 3.8 to 5.0 mEq/l by visit through Month 6 (LT treatment phase).

By Day 14, 8/22 (36.4%) subjects overall achieved serum potassium within target range (3.8 to 5.0 mEq/l); 7/14 (50.0%) subjects in Cohort 1, and 1/8 (12.5%) subjects in Cohort 2 had potassium values within the target range. The proportion of subjects with potassium in the target range generally increased after Day 14 and while on study. At Week 26, 9/11 (81.8%) of subjects in Cohort 1 and 2/9 (22.2%) subjects in Cohort 2 had serum potassium in the target range.

Table 7 Proportion of Subjects Having Central Laboratory Serum Potassium in the Target Range (3.8 to 5.0 mEq/l) Over Time

Visit	Age Group				All Cohorts (N=23)	
	Cohort 1 (Ages 12 to <18): Starting Dose 4.2 g/day (N=14)		Cohort 2 (Ages 6 to <12): Starting Dose 2 g/day (N=9)			
	n/n_{visit} (%)	95% CI[1]	n/n_{visit} (%)	95% CI[1]	n/n_{visit} (%)	95% CI[1]
In target range at:						
Baseline[2]	0/14	0.0, 23.2	1/8 (12.5)	0.3, 52.7	1/22 (4.5)	0.1, 22.8
Day 14	7/14 (50.0)	23.0, 77.0	1/8 (12.5)	0.3, 52.7	8/22 (36.4)	17.2, 59.3
Week 3	7/14 (50.0)	23.0, 77.0	2/8 (25.0)	3.2, 65.1	9/22 (40.9)	20.7, 63.6
Week 26	9/11 (81.8)	48.2, 97.7	2/9 (22.2)	2.8, 60.0	11/20 (55.0)	31.5, 76.9

1 Exact binomial (Clopper-Pearson) CIs.
2 Baseline value is the last non-missing central laboratory value collected before the date and time of first dose of patiromer.
Notes: Percentages are based on the number of subjects with a non-missing potassium value at the study visit, represented by n_{visit}.
Serum potassium data on or after the date of initiation of dialysis are excluded.
CI=Confidence interval; N=Subjects in a cohort; n=Subjects with observation.

The results of the secondary analysis are in line with those of the primary efficacy analysis. While there was a greater proportion of responders in the older cohort, only 50% of subjects could be classified as being responders by the time of the primary analysis. This proportion increased to 81% by the end of the study at week 26.

In Cohort 2, only 1 of 8 patients (12.5%) were responders at Day 14, slightly increasing to 2 of 9 patients (22%) by week 26. These results are not suggestive of significant efficacy in patients below 12 years.

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

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

Not applicable

2.6.5.6. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant presented the results of an open label multiple-dose, single arm pharmacology, efficacy and safety trial of patiromer in paediatric patients from 6 to 18 years with hyperkalaemia. The study was conducted in accordance with an agreed PIP and had been found to be compliant with the key binding elements contained in that PIP.

The primary endpoint of the study was to assess change from baseline in serum potassium levels at Day 14, with secondary efficacy endpoints being measured at Week 3 and Week 26. Additional secondary efficacy endpoints related to the proportion of patients achieving a defined clinical response at Day 14, week 3 and week 26. Responders were defined as those achieving normokalaemia at that timepoint.

The study was initially designed to sequentially recruit patients from 3 age cohorts. Cohort 1 included patients from 12 to 18 years, Cohort 2 included patients from 6 to 12 years, and Cohort 3 included patients from 2 to 6 years. Each cohort was to include a minimum of 12 patients, with the possibility to extend this to 18 patients should adjustments of the starting dose of the medicine be deemed necessary by an independent DSMB. Delays and difficulties in recruitment eventually led to the agreed decision to remove Cohort 3 from this study, to be included instead in a future study. In addition, these recruitment difficulties resulted in only 9 patients being recruited into Cohort 2, while 14 patients were successfully recruited into Cohort 1. The applicant attempted to mitigate the reduction in patient numbers by conducting an extrapolation Pop PD study to bridge the results from the Phase 2 study with those previously obtained during their adult development. This was considered possible due to the similarity of the mechanism of action in both adults and children. Overall, the pivotal study appears to have been well conducted and there are no obvious concerns from a GCP perspective.

The results of the primary efficacy analysis showed a reduction in serum potassium from baseline in both cohorts, although the reduction was significantly higher in older children than younger. This reduction increased over the duration of the study, with a maximal reduction occurring at Week 26.

By Day 14, potassium levels decreased in both cohorts; mean (SD) potassium change from baseline was -0.50 (0.542) mEq/l in Cohort 1 and -0.14 (0.553) mEq/l in Cohort 2.

At Week 3, mean (SD) potassium change from baseline was -0.49 (0.514) mEq/l in Cohort 1 and -0.11 (0.157) mEq/l in Cohort 2.

At Week 26, mean (SD) potassium change from baseline was -1.08 (0.736) mEq/l in Cohort 1 and -0.50 (1.020) mEq/l in Cohort 2.

Similarly, there was a lower number of defined responders in younger patients than in older, with only 22% of patients in Cohort 2 achieving normokalaemia.

The applicant acknowledged that the initial starting dose for patients in Cohort 2 was too low, and this contributed to the delay in achieving clinically significant reductions in serum potassium levels until sufficient up-titration of the dose was carried out. It is not clear what the reason was for this age-related difference in the necessary starting dose for younger patients but given the need to titrate the dose of the product to serum potassium levels, this does not represent an issue in practice. This assertion is supported by the data in the clinical study and is accepted. However, it remains unclear as to why this difference occurred and this in turn undermines the ability to extrapolate efficacy from older to younger patients using the Pop PD study.

This difficulty has been acknowledged by the applicant who eventually restricted the indication to patients above 12 years. This was noted and agreed by the CHMP.

Efficacy data and additional analyses

The applicant provided the results of an extrapolation study aimed at showing that the data in children are similar to those in adults in order to further support the claim that the product is likely to be efficacious in children. Further assessment of this extrapolation study can be found in the Clinical Pharmacology section.

2.6.7. Conclusions on the clinical efficacy

Based on the results of the conducted clinical study, it can be concluded that Veltassa can be considered efficacious in the treatment of hyperkalaemia in children above 12 years of age and hence, the extension of indication to patients of 12-17 years old can be granted.

The results of the week 12 efficacy analysis in children between 6 and 12 years were less convincing. The applicant has asserted that these results were likely as result of an incorrect starting dose in that cohort, but that the results improved once an appropriate up-titration of the dose occurred. While this might be the case, the fact that the extrapolation exercise is deemed unreliable limits the reliability of these evidence in supporting an indication in that age cohort. This difficulty has been acknowledged by the applicant who agreed to restrict the indication to patients above 12 years, while carrying out further clinical trials in the population below 12 years.

2.6.8. Clinical safety

Veltassa (patiromer sorbitex calcium) received marketing authorisation in the EU for the treatment of hyperkalaemia in adults in July 2017. The applicant submitted a Type II variation category C.1.6.a to extend the approved therapeutic indication to patients aged 6 to less than 18 years of age. This has been grouped together with the extension application for the new strength, 1 g powder for oral suspension, for use in paediatric patients in line with Article 7.2 of Commission Regulation (EC) No 1234/2008. However, during the assessment of the procedure, the applicant has revised the proposed extension of indication to include only adolescents aged 12 to 17 years, given the limited clinical data and uncertainties regarding the population PD model and dose-response in subjects aged 6 to <12 years.

In support of the proposed extension of indication of patiromer to paediatric patients 12 to 17 years, the following data were provided:

- Study RLY5016-206p: The pivotal study in 23 paediatric subjects 6 to <18 years of age with HK due to chronic kidney disease (CKD)
- A pharmacodynamic modelling and simulation study with both pivotal studies in adult subjects and Study RLY5016-206p
- Supportive safety data from patiromer off-label use in paediatric patients 1-17 years of age and from literature research on drugs used to treat HK

2.6.8.1. Patient exposure

In Study RLY5016-206p, a total of 34 participants were screened in 18 sites in 7 countries. A total of 23 paediatric patients, from 6 years and above were included. Considering the new revised indication, Cohort 1 subjects aged 12 to <18 years are the most relevant. However, safety data from all 23 subjects in both cohorts are taken into account in this safety assessment.

In terms of the enrolled population, all 23 subjects had CKD. In Cohort 1 (subjects aged 12 <18 years), 9 subjects had congenital anomalies of the kidney and urinary tract, and 1 subject had glomerular disorder. In Cohort 2, 5 had CKD due to congenital anomalies of the kidney and urinary tract, 2 due to glomerular disorder and 1 due to hypertension. 2 patients had received a renal transplant, 1 in each cohort. No patients were on dialysis. Subjects were required to have serum potassium values between 5.1 and < 6.5mEq/L assessed as two separate measurements performed on separate days for enrolment. All subjects received at least 1 dose of patiromer. All subjects completed the Day 14 visit and 91% (21/23) completed the week 26 visit, with 2 subjects in Cohort 1 withdrawing before the Week 26 visit, with reason provided as 'Subject withdrawal'.

Actual prescribed patiromer dose over time

In Cohort 1, the starting dose was 4.2 g/day patiromer. The most often prescribed patiromer dose was 4.2 g/day. The patiromer prescribed dose increased over time and the maximum prescribed patiromer dose in Cohort 1 was 25.2 g/day, prescribed for 1 subject at Weeks 10 and 14, and for 2 subjects at Weeks 18 and 22.

In Cohort 2, the starting dose was 2.0 g/day patiromer. The most often prescribed patiromer doses were 2.0 g/day, 4.0 g/day, and 6.0 g/day. The patiromer prescribed dose increased over time and the maximum dose in Cohort 2 was 12.0 g/day, prescribed for 2 subjects at Week 14, and for 3 subjects at Week 18 and Week 22.

The maximum duration of exposure to patiromer in the study was 6 months. In total 13 subjects, 8 in Cohort 1 and 5 in Cohort 2, were exposed to patiromer for up to 6 months.

Table 8. Post-hoc analysis of EMERALD1: Study Treatment Duration in Days and Weeks

Treatment Duration (Safety Population)

Characteristics	Age Group: Cohort 1 (Ages 12 to <18): Starting Dose 4.2 g/day (N=14)	Cohort 2 (Ages 6 to <12): Starting Dose 2 g/day (N=9)	All Cohorts (N=23)
Treatment Duration (Days)			
n	14	9	23
Mean (SD)	173.1 (29.30)	181.0 (5.50)	176.2 (23.11)
SE	7.83	1.83	4.82
Median	183.0	182.0	183.0
Q1, Q3	176.0, 184.0	175.0, 187.0	175.0, 186.0
Min, Max	76, 189	175, 187	76, 189
Treatment Duration (Weeks)			
n	14	9	23
Mean (SD)	24.72 (4.186)	25.86 (0.786)	25.17 (3.301)
SE	1.119	0.262	0.688
Median	26.14	26.00	26.14
Q1, Q3	25.14, 26.29	25.00, 26.71	25.00, 26.57
Min, Max	10.9, 27.0	25.0, 26.7	10.9, 27.0

Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SE = standard error.
Treatment duration (days): Date of last treatment exposure – date of first treatment exposure +1.
Source: Post Hoc Analyses of EMERALD 1 study Table 1

As specified in the protocol, the study consisted of the following phases: Screening/Day 1 followed by 14-day PD/dose finding phase, 24-week LT treatment phase, and a 2-week follow-up period consisting of 1 follow-up visit and 1 follow-up phone call. Following the 26-week visit, patiromer was discontinued as study treatment and thus the serum potassium measurements collected at the safety follow-up visit were assumed to have been taken whilst off patiromer, thus allowing to evaluate the impact of patiromer discontinuation in this population. During the procedure, it was clarified that some subjects may have received patiromer as standard of care treatment after Week 26, although this was not documented. Therefore, some uncertainty exists with interpreting the serum potassium values for subjects at Follow up visit 1 and 2 after patiromer was discontinued. This is relevant for considering whether any rebound effect of patiromer discontinuation can be assessed. Based on the available data and assuming most subjects did not receive patiromer off-label following its discontinuation on the study, in Cohort 1, there seemed to be a slight decrease in mean serum potassium levels at follow up visit 1 compared to last on treatment value, and a slight decrease at Follow up visit 2. In Cohort 2, at both follow-up visits mean serum potassium was increased compared to last on treatment value. However, the number of subjects is considered too low to draw any firm conclusions. The SmPC already includes an appropriate warning in section 4.4 regarding patiromer discontinuation and now specifically includes that *"There is limited information on serum potassium levels in paediatric patients on patiromer discontinuation"* to highlight the lack of available data.

This highlights the necessity of Study 2, proposed in the PIP, that would include 4 weeks of treatment with study drug followed by a 4-week randomised withdrawal phase to continued treatment or placebo. The objective of Part B of Study 2, *"To evaluate the effect of withdrawing patiromer calcium on serum potassium control in children with CKD,"* is considered highly relevant and could provide more information on serum potassium levels in paediatric patients following patiromer discontinuation. The applicant's proposal to delete Study 2 from the PIP is thus not supported. Study 2 should be conducted as outlined in the agreed PIP and all treatment received following patiromer discontinuation should be carefully recorded for all subjects. The applicant may consider reducing the total number of subjects proposed in Study 2 maintaining particular emphasis on subjects below 12 years, in whom benefit risk has yet to be established, whilst also increasing

subject numbers in Study 3 as highlighted above, in order to generate more comprehensive long term safety data. The applicant committed to assess CHMP's proposal and will submit a PIP modification request to the PDCO.

2.6.8.2. Adverse events

The safety data is considered limited due to 23 subjects aged 6-17 years being included in the pivotal study. For the population aged 12 to 17 years in the restricted indication, 14 subjects were included in the study in Cohort 1.

Considering the intended duration of use for long term treatment of hyperkalemia, it was highlighted that long term safety data is limited with only 13 subjects having received treatment for up to 6 months. The applicant in their response to CHMP's questions discussed that ICH E1 requirements had been met for the adult indication, with 149 adults treated for >/=1 year at time of approval, but that it would not have been feasible to fulfil such requirements in the paediatric population. This argument can be accepted. However, the available data is still considered limited to characterise long term safety in this population. It is acknowledged that these data do not raise any new specific safety concerns and are in line with the safety profile (predominantly GI ADRs and electrolyte disturbances) as was observed in adult population.

Considering that patiromer could be used chronically for many years in a paediatric population, depending on the cause of hyperkalemia and in particular when an indication in a younger population below 12 years had been considered, the applicant was asked to discuss the feasibility of conducting a category 3 pharmacovigilance study to evaluate longer term safety in this population. The applicant concluded that a PASS study would not be feasible, highlighting also recruitment challenges encountered in this setting. However, the applicant noted that study 3 as included in the current agreed PIP will include a 52 week-long term safety extension part allowing to evaluate longer term safety in the paediatric population. The conduct of this long-term safety extension part is strongly supported. Including an additional cohort of subjects from 6 to <12 years in Study 3 to further investigate the efficacy and safety of Veltassa in this age group is also supported. It is highly recommended to increase the total number of subjects enrolled in Study 3 and to define a minimum number of subjects that would be included within the 52-week safety extension period that would allow meaningful data for longer term safety evaluation in the paediatric population to be generated. In the meantime, the applicant has updated the SmPC to highlight the limited long-term data available specifically in the paediatric population. Section 4.4 of the SmPC states that *"Clinical trials in paediatric patients have not included exposure longer than 6 months. Therefore, treatment beyond 6 months should be done with caution in adolescents aged 12 to 17 years."* To better characterise safety in this population, the applicant proposes to extend follow up of SAEs in the target population below 18 years with follow-up performed a minimum of 3 times for up to 1 year and also to specifically discuss all paediatric safety data received within PSURs.

Based on the safety data that is available, the adverse event profile in the paediatric population (particularly subjects 12-<18 years), is broadly similar to that observed in the adult setting, principally GI related AEs and electrolyte abnormalities that included hypokalaemia, hypomagnesemia and hypercalcemia. No treatment related severe AEs and no SAEs were reported in paediatric subjects.

The most frequently (≥5 subjects) reported TEAEs by MedDRA SOC were GI Disorders (6/23 subjects, all in Cohort 1) and Infections and Infestations (2 subjects in Cohort 1 and 3 subjects in Cohort 2). Infections and Infestations and Metabolism and Nutrition Disorders had a similar incidence between treatment groups.

The most frequently (≥2 subjects) reported TEAEs by MedDRA PT were diarrhoea, nasopharyngitis, oropharyngeal pain and renal impairment each reported in 3/23 subjects; and flatulence, nausea, decreased appetite, hypokalaemia, anaemia, each reported in 2/23 subjects.

The majority of TEAEs (see Table 9) were mild or moderate in severity. Moderate TEAEs were reported for 9/23 subjects (7/14 subjects in Cohort 1 and 2/9 subjects in Cohort 2).

Table 9. Summary of Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population, N=23)

System Organ Class/ Preferred Term[1]	Age Group		All Cohorts (N=23)
	Cohort 1 (Ages 12 to <18 years) Starting Dose 4.2 g/day (N=14)	Cohort 2 (Ages 6 to <12 years) Starting Dose 2.0 g/day (N=9)	
Subjects with at least 1 reported treatment-related TEAE	3 (21.4)	1 (11.1)	4 (17.4)
Gastrointestinal disorders	2 (14.3)	0 (0.0)	2 (8.7)
Constipation	1 (7.1)	0 (0.0)	1 (4.3)
Diarrhoea	1 (7.1)	0 (0.0)	1 (4.3)
Flatulence	1 (7.1)	0 (0.0)	1 (4.3)
Frequent bowel movements	1 (7.1)	0 (0.0)	1 (4.3)
Metabolism and nutrition disorders	1 (7.1)	1 (11.1)	2 (8.7)
Hypokalaemia	1 (7.1)	1 (11.1)	2 (8.7)
Investigations	1 (7.1)	0 (0.0)	1 (4.3)
Blood calcium increased	1 (7.1)	0 (0.0)	1 (4.3)

2.6.8.3. Serious adverse event/deaths/other significant events

No serious adverse events or deaths was reported in this study. No significant TEAE, i.e., no TEAE leading to study drug discontinuation, has been reported in this study.

TEAEs resulting in dose reduction and/or interruption in Study RLY5016-206p

Three subjects experienced a total of 5 AEs that led to study drug reduction or interruption. None of these events were considered serious, all events resolved and patiormer was restarted/dose reduced in each case.

Adverse Events of Special Interest

These included gastrointestinal events, renal function events and allergic reactions.

Overall, TEAEs of special interest were reported for 8/23 subjects (all in Cohort 1). The following events (by MedDRA SOC) were reported: GI events were reported for 6 subjects (all in Cohort 1), renal function events were reported for 3 subjects (all in Cohort 1). The GI events by MedDRA PT were diarrhoea (3 subjects), flatulence (2 subjects), nausea (2 subjects), and abdominal pain, constipation, dyspepsia, and frequent bowel movements reported for 1 subject each, and were all mild to moderate in severity. No TEAEs of allergic reactions were reported.

GI AEs: The principal site of action of patiromer is the gut and the most common AEs observed in the adult safety database for patiromer were in the GI SOC. This pivotal study in paediatric subjects, RLY-5016-206p, had the following exclusion criterion included, similar to adult studies:

A history of or current diagnosis of a severe GI diagnosis or surgery that could affect GI transit of the drug (e.g., a severe swallowing disorder, uncorrected pyloric stenosis, intussusception, any other intestinal obstruction (e.g., Hirschsprung disease, chronic intestinal pseudo-obstruction, clinically significant postsurgical abdominal adhesions) or any gut-shortening surgical procedure prior to screening).

Therefore, no patients with severe GI diagnosis or previous surgery that could affect GI transit were included. In the paediatric population, no severe GI AEs occurred in the RLY-5016-206p study. GI events were all mild to moderate in severity, diarrhoea (3 subjects), flatulence (2 subjects), nausea (2 subjects), and abdominal pain, constipation, dyspepsia, and frequent bowel movements reported for 1 subject each. It is noted all GI events occurred in Cohort 1 only.

2.6.8.4. Laboratory findings

The protocol defined the following clinical laboratory outcomes as secondary safety endpoints:

- Changes from baseline in serum chemistry including serum potassium, serum magnesium, serum calcium, serum phosphate, and serum fluoride.
- Changes from baseline in haematology

Serum Potassium

During the study subjects had potassium levels monitored at Day 1, Day 3, Day 7 and Day 14 and then at Week 3, 5, 7, 10, 14, 18, 22 and 26.

- Serum potassium <3.0 mEq/l was not reported for any subjects throughout the study.
- Serum potassium <3.5 mEq/l was reported at Week 26 for 1 subject in Cohort 2.
- Serum potassium <3.8 mEq/l was reported at Week 26, for 2 subjects overall (1 subject in each cohort).
- Serum potassium >5.0 mEq/l was reported at baseline for all subjects in Cohort 1 and for 7/8 subjects in Cohort 2. At Day 14, serum potassium >5.0 mEq/l was reported for 7/14 subjects in Cohort 1 and for 7/8 subjects in Cohort 2. At Week 26, serum potassium >5.0 mEq/l was reported for 1/11 subjects in Cohort 1 and 6/9 subjects in Cohort 2.
- Serum potassium >/=5.5 mEq/l was reported at baseline for 7/14 subjects in Cohort 1 and 5/8 subjects in Cohort 2. At Day 14, serum potassium >/=5.5 mEq/l was reported 3/14 subjects in Cohort 1 and 2/8 subjects in Cohort 2. At Week 26, serum potassium >/=5.5 mEq/l was reported for 1/11 subjects in Cohort 1 and 3/9 subjects in Cohort 2.

Serum Magnesium

At baseline, the mean (SD) serum magnesium values were 2.23 (0.401) mg/dl in Cohort 1 and 2.57 (0.354) mg/dl in Cohort 2. By Day 14, magnesium levels decreased mildly in both cohorts; mean (SD) magnesium change from baseline was -0.14 (0.195) mg/dl in Cohort 1 and -0.16 (0.362) mg/dl in Cohort 2. At Week 26, mean (SD) magnesium change from baseline was -0.24 (0.350) mg/dl in Cohort 1 and -0.50 (0.335) mg/dl in Cohort 2. No subjects in the study (at any time point) had serum magnesium <1.4 mg/dl.

Serum Calcium

At baseline, the mean (SD) serum calcium values were 9.44 (0.750) mg/dl in Cohort 1 and 9.38 (0.741) mg/dl in Cohort 2. By Day 14, calcium levels remained at the same level in both cohorts; mean (SD) calcium change from baseline was -0.16 (0.427) mg/dl in Cohort 1 and -0.04 (0.481) mg/dl in Cohort 2. At Week 26, mean (SD) calcium change from baseline was -0.08 (0.918) mg/dl in Cohort 1 and -0.24 (1.565) mg/dl in Cohort 2.

• Serum calcium >10.2 mg/dl was reported at baseline for 2/14 subjects in Cohort 1 and 1/9 subjects in Cohort 2. At Day 14, serum calcium >10.2 mg/dl was reported for 1 subject in Cohort 2. At Week 26, serum calcium >10.2 mg/dl was reported for 3/12 subjects in Cohort 1 and 2/9 subjects in Cohort 2.

• Serum calcium >11.0 mg/dl was reported for a 1 subject in Cohort 2 at Week 26.

• Serum calcium >/=12.0 mg/dl was not reported for any subject throughout the study.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Not applicable

2.6.8.7. Immunological events

Not applicable

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable

2.6.8.9. Discontinuation due to adverse events

No subjects specifically discontinued due to adverse events based on investigator report.

2.6.8.10. Post marketing experience

Patiromer is approved for adults in 39 countries: EU/EEA (30 countries), US, Switzerland, the UK, Australia, Canada, Israel, United Arab Emirates, Saudi Arabia, and Kuwait for the treatment of hyperkalaemia. Cumulatively until 31 August 2022, patient exposure of 1,424,766 cartons (30 sachets per carton) of Veltassa powder for oral suspension were commercially dispensed, corresponding to 118,704 patient-years since the international birth date of Veltassa on 21 October 2015.

Patiromer was not approved for paediatric use in any region prior to this application.

Off-label Use Cases in paediatric patients: Cumulatively, there were 41 off-label use cases in paediatric patients: 22 from post-marketing (majority from Veltassa Konnect study, a patient support programme that solicits information and updates on insurance, refills, reimbursements, and delivery) and 19 spontaneous

cases. In subjects with hyperkalemia aged 6 to <18 years, there were 32 off-label use cases reported, 7 cases with AEs: 2 serious (blood potassium increased (1) and constipation and hospitalisation (1)) and 5 non-serious. In subjects with hyperkalemia aged < 6 years there were 9 off-label use cases reported, 4 with Aes, 2 were non-serious (blood calcium increased (1) and diarrhoea (1)) and 2 serious (dialysis (1) and death (1)).

The more common frequently reported AEs (>/=2) associated with off-label use were constipation (2, 4.9%), diarrhoea (2, 4.9%) and nausea (2, 4.9%).

The off-label use cases are limited in terms of the safety information they provide, in particular no specific information on causality assessment related to patiromer was provided. However, no specific new safety concerns emerged.

2.6.9. Discussion on clinical safety

Veltassa has been authorised for treatment of hyperkalaemia in adults in the EU since 2017.

The applicant initially submitted a type II variation to extend the approved therapeutic indication to patients aged 6 years of age and older with a line extension to a 1g patiromer presentation. However, following the discussion on the uncertainties raised regarding the benefit-risk in the lower age group by the CHMP mainly due to low number of patients in this group, it was proposed to extend the currently approved indication to adolescents aged 12 to 17 years, grouped together with the extension application for the new strength, 1 g powder for oral suspension, for use in the paediatric patients.

Pivotal study: The primary source of safety data for the proposed extension of indication for paediatric patients 12 years and above is derived from a single global open label multiple dose study, Study RLY5016-206p (EMERALD) providing data from 23 paediatric subjects 6 to <18 years of age with HK due to CKD. There was a higher proportion of patients in Cohort 1: 12 years and above (n=14) *vs* those patients in Cohort 2: 6 years - <12 years (n=9) enrolled. Whilst extrapolation of safety data from adults to children was considered possible for subjects from 12 years and above, due to greater similarities physiologically and the fact that efficacy has been demonstrated, such extrapolation was considered more uncertain in subjects from 6 to <12 years, in whom efficacy has not been conclusively demonstrated and for whom uncertainty remains regarding the optimal dose. The indication was revised to include only adolescents from 12 to 17 years. The applicant plans to further investigate the use of patiromer in subjects aged 6 to <12 years as part of the agreed PIP.

In the adult clinical development programme, 239/2135 subjects (11.2%) received patiormer for at least 1 year. No paediatric subjects had long term exposure of 1 year or more. As such, the safety of long-term use in the paediatric population is unknown. The maximum duration of treatment was 6 months in 13/23 (57%) of paediatric subjects. The absence of longer-term data beyond 26 weeks in children is considered a limitation of the data, especially as patiromer could be intended for chronic use, in particular for subjects with CKD with limited access to paediatric renal transplantation. In terms of considering longer term effects of patiromer in children, it is noted by the applicant that patiromer is not systemically absorbed, thus limiting potential systemic toxicity and cumulative effects. The negligible systemic absorption of patiromer is acknowledged by the CHMP, and in general, the safety profile observed in the paediatric subjects was considered similar to that observed in adults. However, depending on the underlying cause of hyperkalaemia and availability of alternative treatments, patiromer may be used long term in some paediatric patient groups, with no maximum duration of treatment as specified in the SmPC. Therefore, it is considered

important to better characterise long term safety. The applicant was requested to discuss the feasibility of conducting a category 3 pharmacovigilance study to further characterise long term safety. However, based on recruitment challenges experienced in the Study RLY5016-206p and difficulties with estimating the prevalence of hyperkalaemia in a paediatric population, the applicant concluded such a long-term safety study would not be feasible. In terms of follow-up measures, the applicant proposes to perform the follow-up (minimum of 3 times) on all SAEs extended up to 1 year, which is supported, and all paediatric safety data received will be included and discussed in the PSURs. The applicant also highlights that Study 3 in the PIP, EMERALD 2, will be amended to include patients from birth to <12 years of age, and subjects will be offered to participate in a 4-week PD/dose finding phase followed by a 52-week safety extension period. In this extension period, safety assessment will be conducted as per standard of care with a minimum of collection of blood potassium, blood fluoride and AE assessment. The safety extension period would add additional long-term data for paediatric patients and is strongly supported. The applicant's proposal to include an additional cohort of subjects from 6 to <12 years in Study 3 is also supported. At present the proposed number of subjects in Study 3 will be only 12 (or 21 if subjects 6-<12 added), and thus, it is highly recommended to increase the total number of subjects enrolled in this study and to define a minimum number of subjects that would be included within the 52-week safety extension period, which would allow longer term safety data to be generated, for the paediatric population. In the meantime, the SmPC has also been updated, to highlight that treatment beyond 6 months should be done with caution in adolescents aged 12 to 17 years which reflects the lack of long-term safety data at this time. The RMP also includes as missing information, long term treatment in subjects <18 years.

Revisions were made to the proposed SmPC as requested, clarifying that the duration of treatment should be individualised by the treating physician based on the need of serum potassium management. It is also specified that serum potassium should be monitored when clinically indicated and there is cross-reference to section 4.4 which also provides warning on discontinuation of patiromer. The SmPC was updated to also reflect that there is limited information on serum potassium levels in paediatric patients on patiromer discontinuation. This highlights the necessity of the study 2 outlined in the PIP that would include 4 weeks of treatment with study drug followed by a 4-week randomised withdrawal phase to continued treatment or placebo. The objective of Part B of Study 2 (to evaluate the effect of withdrawing patiromer calcium on serum potassium control in children with CKD) is considered highly relevant and could provide more information on serum potassium levels in paediatric patients following patiromer discontinuation. The applicant's proposal to delete Study 2 from the PIP is thus not supported by the CHMP. The applicant may consider reducing the total number of subjects proposed in Study 2 with particular emphasis on subjects below 12 years, in whom benefit risk has yet to be established, whilst also increasing subject numbers in Study 3 as highlighted above, in order to generate more comprehensive long term safety data. The applicant has committed to assess this proposal and will submit a request for modification to PDCO.

Adverse Events: In total 65.2% of the enrolled population (15/23) had TEAEs, the majority of which were mild or moderate in severity. There were no TEAEs leading to death or serious TEAEs reported. There were 7 study drug-related TEAEs in 4 subjects, 3 in Cohort 1 and 1 in Cohort 2. Two of these subjects experienced drug related GI TEAEs both, in Cohort 1. Two patients in Cohort 1 withdrew prematurely before the Week 26 visit; both experienced TEAEs, although investigator had assessed these as not related to patiromer. The most frequently (≥2 subjects) reported TEAEs by MedDRA PT were diarrhoea, nasopharyngitis, oropharyngeal pain and renal impairment each reported in 3/23 subjects; and flatulence, nausea, decreased appetite, hypokalaemia and anaemia, each reported in 2/23 subjects. The majority of TEAEs were mild or moderate in severity.

*Treatment related TEAEs***:** In the study, there were 7 treatment-related TEAEs reported in 4 subjects, 3/14 subjects in Cohort 1 and 1/9 subjects in Cohort 2. The treatment-related TEAEs were in the MedDRA SOC of GI Disorders (2/14 subjects in Cohort 1), Metabolism and Nutrition Disorders (1 subject in each cohort), and Investigations (1/14 subject in Cohort 1). TEAEs related to treatment by MedDRA PT were constipation, diarrhoea, flatulence, frequent bowel movements, and blood calcium increased (1 event each, all in Cohort 1) and 2 events of hypokalaemia (1 subject in each cohort). All treatment related AEs were considered non-serious and all graded mild to moderate in severity. In Cohort 1, 2 subjects received the maximum dose of 25.2 g/day. In Cohort 2, 3 subjects received the maximum dose of 12.0 g/day. No related TEAEs were observed at maximum dose of treatment.

TEAEs resulting in dose reduction and/or interruption: There were 3 subjects who experienced study drug dose reduction and/or interruption, for treatment related TEAEs, 2 patients in Cohort 1 and 1 patient in Cohort 2. All TEAEs resolved and patiromer was continued at a reduced dose or restarted in each case.

TEAEs of Special Interest: There were 14 TEAEs of special interest reported in 8 subjects, all in Cohort 1. GI events were reported for 6 subjects (all in Cohort 1) and renal function events reported for 3 subjects (all in Cohort 1).

GI AEs: The principal site of action of patiromer is the gut and the most common AEs observed in the adult safety database for patiromer were in the GI SOC. This study in paediatric subjects, excluded subjects with a history of a severe GI diagnosis or surgery that could affect GI transit of a drug, similarly to adult studies.

At time of original Veltassa approval in the adult population, an important potential risk of 'Increased risk of intestinal perforation in patients with current or history of severe GI disorders' was included in the RMP due to the fact that intestinal perforation has been reported with other polymers that act in the gastrointestinal tract.

The SmPC was updated during the procedure to highlight the warning on GI disorders in section 4.4 is also relevant for the paediatric population:

"*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 patiromer should be carefully evaluated in adult and paediatric patients with current or history of severe gastrointestinal disorders, before and during treatment."*

In the paediatric population in Study RLY5016-206p, no severe GI AEs occurred in the RLY-5016-206p study. GI events which occurred were all mild to moderate in severity; diarrhoea (3 subjects), flatulence (2 subjects), nausea (2 subjects), and abdominal pain, constipation, dyspepsia, and frequent bowel movements reported for 1 subject each. It is noted all GI events occurred in Cohort 1 only. There was no explanation for the seeming lack of GI related AEs reported for Cohort 2 other than that the data set available for subjects 6 to <12 years of age are limited. It is also considered that the starting dose was lower at 2.0g and this may have reduced the AE occurrence. The 6- <12 years old patients will be evaluated in a separate study, as per the PIP.

From the above review, 13 TEAEs in the GI SOC were reported for 6 subjects, all in Cohort 1. Most events 9/13, were deemed unrelated to patiromer, despite similar GI AEs being known as AEs related to patiromer in the adults. The applicant stated that causality assessment was provided by the investigators and reviewed by the applicant and the DSMC, who did not have any objections on the causality assessments and agreed that the events were due to other factors such as multiple comorbidities and/or polypharmacy. The SmPC

appropriately highlights GI ADRs as known. GI ADRs in all age groups will be specifically followed up within the PSUR, as agreed by the applicant.

Given the known risks associated with similar potassium binders related to gastrointestinal motility, the MAH was requested to discuss based on an up-to-date analysis of their safety database whether any AEs of decreased GI motility were encountered or whether decreased GI motility occurred in association with any GI AEs and whether any AEs were observed in association with severe constipation or impaction. The applicant concluded that they found no evidence of AEs of decreased GI motility or decreased GI motility in association with any GI AEs and any AEs in association with severe constipation or impaction related to Veltassa. It can be agreed that there was no new specific evidence that would necessitate updating the product information. The current warning in section 4.4, as well as the inclusion of ADRs in SOC gastrointestinal in section 4.8 at present, is considered adequate. However, the applicant will keep gastrointestinal motility and any associated AEs under review and discuss these as a special topic in the regular PSURs for Veltassa.

The renal function events (by MedDRA PT) were renal impairment, reported for 3 subjects and were assessed as not related to study drug. Considering this was a population with baseline CKD this seems reasonable.

No events from SOC Allergic reactions occurred. Given the limitations of the safety database this will also be followed as a special topic in the PSUR.

Laboratory findings: Changes from baseline in serum chemistry including serum potassium, serum magnesium, serum calcium, serum phosphate, and serum fluoride were included as secondary safety endpoints.

Serum potassium: The enrolled participants were required to have hyperkalemia due to CKD in order to be eligible with potassium from 5.1 to <6.5 mEq/L. Most subjects had serum potassium </=6.0mEq/L, with the highest serum potassium of 6.2mEq/L at enrolment. The mechanism of action is to lower serum potassium, and during the study most subjects experienced a serum potassium reduction as the dose was titrated. Hypokalaemia is a known effect of Veltassa, demonstrated also in the adult population, based on its target effect to lower serum potassium. During the study, no subjects experienced a serum potassium <3.0mmol/L. From the presented tables, 1 subject in Cohort 2 experienced a Serum potassium <3.5 mEq/l at Week 26. 2 subjects (1 in each cohort) experienced a serum potassium <3.8 mEq/l at Week 26.

Whilst subjects were required to discontinue patiromer on the study at Week 26, the sponsor did not collect medication use at time of follow up visits. Therefore, it cannot be determined whether any subjects may have received off-label use of patiromer at follow-up. However, for most subjects, it could be assumed that serum potassium measurements were taken at follow up visits whilst off patiromer. The SmPC appropriately highlights the limited information on serum potassium levels in paediatric patients on patiromer discontinuation. Furthermore, the SmPC also states that serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAAS inhibitors or diuretics) and after the patiromer dose is titrated or discontinued.

Serum magnesium: In this study, baseline magnesium levels ranged from 1.5 to 3.0mg/dl at screening day 1. Whilst there was an overall decrease in mean serum magnesium change from baseline in both cohorts, at baseline 9 of 23 subjects had serum magnesium of 2.5mg/dl or above. One subject reported a serum magnesium of 1.4mg/dl at week 14 (magnesium at screening 1.9mg/dl) which recovered by week 26 to 1.5mg/dl. No subjects experienced a serum magnesium <1.4mg/dl. Based on the available data in adults, hypomagnesemia is already considered a 'common' adverse reaction in the SmPC Section 4.8. Section 4.4 already provided information on risk of low magnesium. This section has now been updated to provide the mean decrease in serum magnesium seen in paediatric study also and the SmPC wording has been

strengthened to state serum magnesium should be monitored for at least 1 month after initiating treatment 'and as clinically indicated during treatment'.

Serum calcium: In terms of hypercalcemia, 3 subjects had elevated serum calcium at baseline. At Week 26, serum calcium >10.2 mg/dl was reported for 3/12 and 2/9 subjects, Cohort 1 and Cohort 2, respectively. Only 1 patient in Cohort 2 reported a serum calcium >11.0 during the study, 11.6mg/dL at week 26. This patient had a screening calcium of 10.0mg/dL with high magnesium and high phosphate. At follow-up visit 1 serum calcium had reduced slightly to 10.9mg/dl but was still elevated. Veltassa contains calcium as part of the counterion complex. The SmPC section 4.4 includes wording on the need to monitor calcium serum levels at least 1 month after initiating Veltassa treatment. The longer-term potential impact of elevated serum calcium in a paediatric population however is unknown and the applicant has committed to follow this up as a special topic in the PSUR.

Serum fluoride: Calcium fluoride is a degradation product in the finished product and at time of original assessment in adults the fluoride limit during shelf-life was stated to be in line with the EFSA recommendations for individuals above 15 years. At the time of original assessment, the limits were tightened to actual values observed in stability studies, with the fluoride specifications being 55 ppm at lot release and 175 ppm during shelf-life (3 years at 2 – 8°C with up to 6 months at non-refrigerated conditions (below 25°C) within the overall shelf-life).

The applicant highlights that at low levels, fluoride is important in the development and maintenance of teeth at all ages but is not considered an essential nutrient. In children, dental fluorosis is an undesirable side-effect of excessive fluoride intake during critical periods of amelogenesis of both primary and secondary teeth. The sensitive period ranges up to eight years of age and thus is of less relevance for the proposed population from 12 years and above. Skeletal fluorosis is the major concern related to chronic intake of excess levels of fluoride and needs to be considered in a paediatric population. The applicant notes that skeletal fluorosis developed from dietary sources is practically unknown in Europe, as it would require high fluoride concentration in drinking water. The applicant highlights that as was considered in the safety assessment at time of original MAA, the recommended upper limit of fluoride defined by EFSA panel was 0.12 mg/kg body weight per day or 5 and 7 mg/day for children and adolescents aged 9-14 and 15 years and older, respectively for risk of bone fractures. Based on estimates of the highest daily fluoride exposure of 2.6mg/day, that would potentially occur at the end of shelf life for Veltassa at the highest dose of 25.2g/day, this would still be below the upper limit of fluoride intake recommended by EFSA for both subjects aged 12-15 years (5mg/day) and subjects aged >15 years (7mg/day), noting that these limits do not account for reduced fluoride clearance anticipated to occur due to CKD. This estimate of 2.6mg/day is also considered to be a worst-case scenario, at end of shelf life at the highest dose.

No normal ranges for serum fluoride were provided by the central laboratory in this study. In the paediatric population studied in EMERALD 1, at baseline, the mean (SD) serum fluoride values were 29.8218 (17.53859) ng/ml in Cohort 1 and 47.4184 (39.69090) ng/ml in Cohort 2. By Day 14, mean (SD) fluoride change from baseline was -0.8655 (9.43736) ng/ml in Cohort 1 and 19.5125 (44.53286) ng/ml in Cohort 2. At Week 26, mean (SD) fluoride change from baseline was 9.4705 (13.05864) ng/ml in Cohort 1 and 1.9077 (15.09295) ng/ml in Cohort 2, showing only a small increase overall. Acknowledging the low numbers, the observed increases in mean serum fluoride values appeared low. It is endorsed and considered relevant that the proposed 52-week safety extension period in Study 3 (EMERALD 2) will also include collection of blood fluoride levels and as highlighted, the Applicant is recommended to define a minimum number of subjects that would be included within the 52-week safety extension period that would allow meaningful data for

longer term safety evaluation of this topic to be generated. The applicant has also committed to keeping potential increased exposure to fluoride in a paediatric population under review in future PSURs.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety data is considered limited due to only 23 subjects aged 6-17 years having been included in the pivotal study. The proposed indication was revised to 'Veltassa is indicated for the treatment of hyperkalaemia in adults and adolescents aged 12 to 17 years' and the applicant will further evaluate Veltassa in paediatric subjects aged 6 to <12 years in Study 3 of the PIP.

Based on the available safety data, the adverse event profile in the paediatric population (particularly subjects 12-17 years), is broadly similar to that observed in the adult setting (GI related AEs and electrolyte abnormalities such as hypokalaemia, hypomagnesemia and hypercalcemia). No treatment related severe AEs and no SAEs were reported. No TEAEs led to study drug discontinuation. The safety database is however considered limited due to only 23 subjects aged 6-17 years having been included in the pivotal study, which is highlighted in the SmPC.

The concern related to long-term safety in the paediatric population has also been appropriately highlighted in the SmPC outlining that the data in adolescents aged 12 to 17 years are limited to 6 months exposure and therefore, treatment beyond 6 months should be done with caution in adolescents aged 12 to 17 years. The applicant proposed to follow-up on all SAEs extended up to 1 year. Overall, whilst no new safety concerns have been identified in the paediatric population, the size of the safety database is considered limited. Therefore, it is important that all paediatric safety data should be included and discussed in the respective sections of PSURs. In addition, the proposal that long term safety data will also be generated from the safety extension part of EMERALD 2 (Study 3 in the PIP), is strongly supported. The CHMP recommended to increase the total number of subjects enrolled in this study and to define a minimum number of subjects that would be included within the 52-week safety extension period that would allow meaningful data for longer term safety evaluation in the paediatric population to be generated.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	Hypomagnesaemia/low magnesium
Important potential risks	Increased risk in patients with current or history of hypercalcaemia Increased risk of intestinal perforation in patients with current or history of severe GI disorders
Missing information	Pregnant or lactating women Long-term treatment in patients <18 years old

The applicant proposed the above summary of safety concerns in the RMP Version 2.3 (DLP 01 Aug 2022, dated 6 Nov 2023). Having considered the data in the safety specification, the summary of safety concerns in the RMP is acceptable.

2.7.2. Pharmacovigilance plan

The CHMP considered that the pharmacovigilance plan acceptable.

2.7.3. Risk minimisation measures

Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypomagnesaemia/low magnesium	Routine risk communication SmPC Sections 4.4 and 4.8 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommendation to monitor serum magnesium at least 1 month after initiating Veltassa treatment, and to consider magnesium supplementation in patients who develop low serum magnesium levels. Other routine risk minimisation measures beyond the Product Information: Pack size : Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets. Legal status: Prescription only medicine
Increased Risk in Patients with Current or History of Hypercalcaemia	Routine risk communication: SmPC Section 4.4 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations to use Veltassa for patients at risk of hypercalcaemia following careful assessment of benefit/risk by the prescribing physician. Other routine risk minimisation measures beyond the Product Information: Pack size: Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Legal status: Prescription only medicine

Increased risk of intestinal perforation in patients with current or history of severe GI disorders	Routine risk communication SmPC Section 4.4 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommendation to carefully evaluate the benefit/risk of Veltassa in patients with current or history of severe gastrointestinal disorders, before and during treatment by the prescribing physician. Other routine risk minimisation measures beyond the Product Information: Pack size Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets. Legal status: Prescription only medicine
Use in Pregnant and Lactating Women	Routine risk communication: SmPC Section 4.6 PIL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: These special populations are highlighted in SmPC Section 4.6. There are no data from the use of patiromer in pregnant women, appropriate caution and benefit/risk assessment in treatment decision making by the prescribing physician are addressed in the aforementioned section. Other routine risk minimisation measures beyond the Product Information: Pack size: Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets Legal status: Prescription only medicine
Long-term treatment in patients <18 years old	Routine risk communication SmPC Section 4.2 Routine risk minimisation activities recommending specific clinical measures to address the risk The data in children ages 6 years and older are limited to 6 months exposure Other routine risk minimisation measures beyond the Product Information

	Pack size Veltassa 1 g is available in packs containing 60 sachets. Veltassa 8.4 g is available in packs containing 30, 60 or 90 sachets and multipacks comprising 3 cartons, each containing 30 sachets. Veltassa 16.8 g and 25.2 g are available in packs containing 30, 60 or 90 sachets. Legal status: Prescription only medicine

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7.4. Conclusion

The applicant provided an updated RMP version 2.3.

The CHMP and PRAC considered that the risk management plan version 2.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Veltassa. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

There are several causes of HK in paediatric patients, and as in adults, CKD is by far the most common (>80% of cases). Given the mechanism of action of patiromer, disorders associated with a decreased output or renal clearance of potassium would likely benefit from potassium binding therapies to remove potassium from the body and lower serum potassium levels. Disorders related to increased exogenous intake are better addressed by changes in diet or medications. In endogenous disorders, particularly in the acute setting such as with crush injuries or tumour lysis syndrome, HK is best managed by treatment of the underlying disease, supportive care and measures to rapidly reduce serum potassium levels such as with insulin, beta-adrenergic agonists or dialysis. Factitious HK does not require treatment with potassium-removing interventions.

In patients with CKD, the primary cause of HK is a decrease in renal elimination of potassium, and the risk of HK increases as renal function deteriorates. The use of drugs that block the renin-angiotensin aldosterone system can increase the risk and severity of HK in patients with underlying CKD. Given this class of therapies has been proven to slow progression of renal disease in both adult and paediatric patients with CKD, the management and treatment of HK is critically important.

3.1.2. Available therapies and unmet medical need

Treatment of HK can involve the restriction of potassium through dietary means, avoidance of medicines which further reduce potassium elimination, administration of substances aimed at promoting a shift of potassium from extracellular to intracellular spaces, sequestration, and secondary elimination of potassium through the use of binding agents, and ultimately the removal of potassium through various renal replacement therapies such as dialysis. However, despite these measures there remains an unmet medical need for safe and effective therapies for the treatment of hyperkalaemia in children.

3.1.3. Main clinical studies

The pivotal study EMERALD provided to support this line extension and extension of indication is a Phase 2, Open-Label, Multiple Dose Stud y to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 6 to <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD) (Study 1 from the PIP). This phase 2 study was designed to evaluate the pharmacodynamic effects, safety and tolerability of patiromer in a paediatric population with CKD and hyperkalaemia. The study included 2 treatment phases: Pharmacodynamic (PD)/dose finding phase consisting of an initial 14-day dose finding period followed by an up to 24-week long-term (LT) treatment phase. The primary objective was to assess change from baseline in serum potassium levels to Day 14 following administration of different doses of patiromer administered once daily, whilst safety and tolerability assessment were secondary objective. This was an appropriately designed dose-finding trial to assess the effect of patiromer on the reduction of serum potassium levels in children, from 6 to 18 years with hyperkalaemia.

3.2. Favourable effects

At the time of the primary analysis of the data from EMERALD trial, patients in the older age cohort (12-17y) had a significant reduction (-0.50 mEq/l) in the serum potassium levels from baseline at D14. This effect persisted and increased up to the end of the study at week 26, reaching a maximum of -1.08 mEq/l. In addition, a majority (82%) of patients were classified as responders at the end of the trial. Responders were defined as patients who achieved normokalaemia on treatment. There was a smaller reduction in serum potassium levels in younger patients aged 6 to <12 years, at the end of the trial (-0.50 mEq/l, and a small proportion (22%) of patients were classified as responders at Week 26. As outlined, the indication is being sought only for subjects from 12 years and above, mainly due to the low numbers of patients in the age group 6-12y.

3.3. Uncertainties and limitations about favourable effects

While the results in the older cohort support Veltassa's efficacy, the results in the younger patients at the time of the primary efficacy analysis were less convincing. The initial reduction at Day 14 (primary endpoint) was only -0.14 mEq/l, with only 1 of 8 patients in this cohort being classified as responders. This only rose to 2 of 9 by the end of the trial. The applicant acknowledged that the initial starting dose for patients in Cohort 2 was too low, and this contributed to the delay in achieving clinically significant reductions in serum potassium levels until sufficient up-titration of the dose was carried out.

Assessment of results of Study 1 was proposed to be supported by an extrapolation study, Study 4, in the PIP. However, uncertainties were raised in relation to the acceptability of this modelling approach to enable such extrapolation (see section 2.6.2-2.6.3). This therefore further challenges the limited data from what was originally intended only as a dose finding Phase 2 study. As such, the applicant has proposed to evaluate Veltassa further in subjects aged 6 to <12 years, as part of Study 3 of the PIP and limited the claimed indication to adolescents from 12 to 17 years.

3.4. Unfavourable effects

The primary source of safety data for the proposed extension of indication is derived from the single global open label multiple dose study, Study RLY5016-206p (EMERALD) providing data from 23 paediatric subjects 6 to <18 years of age with HK due to CKD. Overall, no new safety concerns have emerged from the small paediatric population studied in EMERALD. The observed safety profile, in particular in subjects from 12 years and above, appears similar to the adult population.

In total 65.2% of the enrolled population (15/23) had TEAEs, the majority of which were mild or moderate in severity. There were no serious TEAEs reported and no TEAEs leading to death. The most frequently reported TEAEs were in the GI SOC, followed by infections and infestations SOC. The most frequently (≥2 subjects) reported TEAEs by MedDRA PT were diarrhoea, nasopharyngitis, oropharyngeal pain and renal impairment each reported in 3/23 subjects; and flatulence, nausea, decreased appetite, hypokalaemia, anaemia, each reported in 2/23 subjects. The majority of TEAEs were mild or moderate in severity. Moderate TEAEs were reported for 9/23 subjects (7/14 subjects in Cohort 1 and 2/9 subjects in Cohort 2). 1 subject in Cohort 1 experienced a severe, but non-serious TEAE of renal impairment at Day 106, deemed unrelated to treatment.

There were 7 treatment related TEAEs reported in 4 subjects, 3/14 subjects in Cohort 1 and 1/9 subjects in Cohort 2. TEAEs related to treatment by MedDRA PT were constipation, diarrhoea, flatulence, frequent bowel

movements, and blood calcium increased (1 event each, all in Cohort 1) and 2 events of hypokalaemia (1 subject in each cohort). All treatment related AEs were considered non-serious and all graded mild to moderate in severity.

The principal site of action of patiromer is the gut and the most common AEs observed in the adult safety database for patiromer were in the GI SOC. This pivotal study in paediatric subjects, RLY-5016-206p, similar to adult studies, excluded subjects with severe GI diagnosis or previous surgery that could affect GI transit. At time of original approval in the adult population, an important potential risk of 'Increased risk of intestinal perforation in patients with current or history of severe GI disorders' had been included in the RMP due to the fact that intestinal perforation has been reported with other polymers that act in the gastrointestinal tract. In the paediatric population, no severe GI AEs occurred in the RLY-5016-206p study. GI events were all mild to moderate in severity, diarrhoea (3 subjects), flatulence (2 subjects), nausea (2 subjects), and abdominal pain, constipation, dyspepsia, and frequent bowel movements reported for 1 subject each. All GI events occurred in Cohort 1 only. During the procedure, the applicant amended the SmPC to highlight that the warning in Section 4.4 regarding GI disorders equally applies to the paediatric population. The applicant has also committed to follow up and discuss all GI ADRs in all age groups within the PSUR, as well as gastrointestinal motility and any associated AEs as a special topic within the PSUR.

Hypokalaemia is a known adverse effect of treatment with Veltassa, demonstrated also in the adult population. During the study, no subjects experienced a serum potassium <3.0mmol/L. One subject in cohort 2 experienced a serum potassium <3.5 mEq/l at week 26. Two subjects (1 in each cohort) experienced a serum potassium <3.8 mEq/l at Week 26. The SmPC appropriately highlights the need to monitor serum potassium levels as per standard practice when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAAS inhibitors or diuretics) and after the patiromer dose is titrated or discontinued. Based on the available data in adults, hypomagnesemia is already considered a 'common' adverse reaction in the SmPC Section 4.8 for Veltassa. In this study, the AE of hypomagnesemia occurred in 1 subject. Similar instructions for monitoring serum magnesium levels whilst on treatment are also included within the SmPC.

Veltassa contains calcium as part of the counterion complex. The SmPC section 4.4 currently states that 'calcium is partially released which may be absorbed'. At Week 26, serum calcium >10.2 mg/dl was reported for 3/12 and 2/9 subjects, Cohort 1 and Cohort 2, respectively. Only 1 patient in Cohort 2 reported a serum calcium >11.0 during the study, 11.6mg/dL at week 26. The applicant has committed to follow up the important potential risk of hypercalcemia in the paediatric population as a special topic in future PSURs.

3.5. Uncertainties and limitations about unfavourable effects

The principal limitation is the size of the safety database, with only 23 subjects treated aged 6-17 years in a single clinical trial. Thus, despite the safety profile being broadly similar to that observed in the adult population, the low number of subjects treated limits the ability to comprehensively characterise safety in this population. The data for subjects aged 6-<12 years is particularly limited, with only 9 subjects included and the benefit could not be established. Hence, the applicant revised the sought indication to include only adolescents aged 12 to 17 years, during the assessment, which is supported. The pivotal study did not include a comparator arm which also limits safety assessment.

No maximum duration of treatment with patiromer is specified in the SmPC. It is stated that the daily dose should be titrated to reach the desired target range of serum potassium, with advice that "if serum potassium falls below the desired range, the dose should be reduced or discontinued." It is thus understood that

depending on the cause of hyperkalaemia, patients may in some cases require chronic treatment with patiromer. Therefore, a further limitation is the duration of treatment exposure in this population, with only 13 subjects having received 6 months of treatment. The applicant has outlined their position as to why it is not considered feasible to conduct a PASS study, largely due to recruitment challenges encountered with the EMERALD study and projected timelines. The proposal from the applicant that long term safety data will also be generated from the 52-week safety extension part of EMERALD 2 (Study 3 in the PIP), is supported. It is recommended to the applicant to increase the total number of subjects enrolled in this study and to define a minimum number of subjects that would be included within the 52-week safety extension period that would allow meaningful data for longer term safety evaluation in the paediatric population to be generated; subject to discussion with the PDCO. All SAEs will be followed for a minimum of 3 times up to 1 year and all paediatric safety data received should be included and discussed in the respective sections of PSURs. In the meantime, the SmPC appropriately highlights the fact that long term exposure in paediatric subjects is limited and use beyond six months should be done with caution.

In terms of potential class effect, an increased risk of intestinal perforation in patients with current or history of severe GI disorders, had been included as an important potential risk in the RMP at time of approval in the adult population. In the clinical studies in adults and children to date subjects with a history of severe GI disorders have been excluded. No severe GI AEs occurred in the paediatric population, however, such AEs are likely to only be detected in the post-marketing setting and thus require continued monitoring in PSURs. This was agreed by the applicant; GI ADRS in all age groups and in addition GI motility and any associated AEs will be followed-up as a specific topic in future PSURs. The SmPC appropriately highlights the risk of gastrointestinal disorders in section 4.4.

3.6. Effects Table

Table 10. Effects table for Veltassa for the reduction of hyperkalaemia in 12-17 years old patients.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Serum potassium	Reduction from baseline – Day 14 Primary endpoint	mEq	-0.49 – Cohort 1 -0.11 – Cohort 2	N/A	Only 9 patients recruited to cohort 2 (12 planned)	CSR RLY5016-206p
	Reduction from baseline – Week 26 Secondary endpoint	mEq	-1.08 – cohort 1 -0.50 – cohort 2	N/A		
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Cohort 1 Cohort 2	Subjects with at least 1 treatment related TEAE		3 (21.4%) 1 (11%)		Size of the safety database	
Cohort 1	Gastrointestinal disorders -Constipation -Diarrhoea -Flatulence -Frequent bowel movements Metabolism and nutrition disorders -Hypokalemia Investigations -Blood calcium increased		2 (14.3%) 1(7.1%) 1(7.1%) 1(7.1%) 1(7.1%) 1(7.1%) 1(7.1%) 1(7.1%) 1(7.1%)		Size of the safety database	
Cohort 2	Metabolism and nutrition disorders -Hypokalemia		1(11.1%) 1(11.1%)		Size of the safety database Limited AEs reported in Cohort 2	

Abbreviations: NA
Notes: NA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy: Overall, Veltassa is effective in significantly lowering serum potassium levels from baseline in patients over 12 years, with mean decreases of 0.49mEq at Day 14, the date at which the primary endpoint was measured in study RLY5016-206p. These reductions become more pronounced over time, reaching a maximum reduction of 1.1mEq by Week 26. The reductions in patients between 6 and 12 were less pronounced, with only a 0.11 mEq reduction at Day 14, although this did eventually increase to a maximal reduction of 0.5mEq by Week 26. The applicant has acknowledged that the initial starting dose for patients in Cohort 2 was too low, and this contributed to the delay in achieving clinically significant reductions in serum potassium levels until sufficient up-titration of the dose was carried out. The applicant has, however, stated that given the need to titrate the dose of the product to serum potassium levels this higher starting dose would not be an issue in practice. This was not fully accepted by the CHMP, and the applicant limited the indication to use in patients above 12 years until further evidence in younger children can be gathered as part of Study 3 of the PIP.

Safety: From a safety perspective, it is reassuring that no significant safety concerns have been identified in the paediatric population from 6 years of age and above. In general, the overall safety profile has been demonstrated to be broadly similar to the adult population, in which the most common AEs were noted to be gastrointestinal side effects and electrolyte disturbances; hypomagnesemia, hypokalaemia and hypercalcemia having been observed. However, despite this, it is considered a limitation of the safety database that only 23 subjects in total were enrolled.

Whilst extrapolation of safety data from adults to children may be possible for subjects from 12 years and above given greater similarities physiologically and the fact that efficacy has been demonstrated, in subjects from 6 to <12 years there remained considerable uncertainty regarding the optimal dose and the PD modelling approach proposed to support this. As mentioned above, the applicant revised the proposed indication to include only patients from 12 to 17 years and will further evaluate the younger population aged 6 to <12 years in a future study, which is endorsed. In the meantime, all SAEs up to 1 year and all paediatric safety data received should be included and discussed in the respective sections of PSURs. The SmPC now appropriately highlights the fact that long term exposure in paediatric subjects is limited and use beyond six months should be done with caution.

3.7.2. Balance of benefits and risks

In patients above 12 years, efficacy has been demonstrated and is considered clinically relevant. The safety profile has been demonstrated to be similar to the adult population. The most common adverse events are gastrointestinal and electrolyte disturbances. The SmPC reflects this information accordingly. Overall, the balance of benefits versus risks is positive in adolescents from 12 to 17 years. Longer term safety will need to be further characterised in the post-marketing setting, as agreed with the applicant.

3.8. Conclusions

The overall benefit /risk balance of Veltassa can be considered positive for the treatment of hyperkalaemia in adolescents from 12 to 17 years.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of, Veltassa 1 g powder for oral suspension, is favourable in the following indication:

"Veltassa is indicated for the treatment of hyperkalaemia in adults and adolescents aged 12 to 17 years."

The CHMP therefore recommends the extension of the marketing authorisation for Veltassa subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (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.

In addition, CHMP did recommend the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new strength (1 g powder for oral suspension), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of population from 12 to 17 years old for Veltassa based on final results from paediatric study RLY5016-206P (EMERALD); this is a phase 2, open-label, multiple dose study to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer for oral suspension in children and adolescents 2 to less than 18 years of age with chronic kidney disease and hyperkalaemia. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 6.5 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 2.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes.