Summary of Results

Title:	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 <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD)
Clinical Protocol Number:	RLY5016-206p
Investigational Product:	Patiromer for oral suspension
Development Phase of Study:	2
Indication Studied:	Treatment of hyperkalaemia
Date of First Subject First Visit:	6 July 2017
Date of Last Subject Last Visit:	30 April 2021
Study Termination Date:	13 May 2022
EudraCT Number:	2016-002785-31
Sponsor Medical Expert:	Julian Platon, MD, PhD
Sponsor Address:	Vifor Pharma, Inc. 200 Cardinal Way Redwood City, CA 94063, US
Good Clinical Practice Statement:	This study was conducted in compliance with the ICH tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents
Date of Report:	30 September 2022

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Name of Finished Product:	Patiromer for oral suspension
Name of Active Ingredient:	Patiromer sorbitex calcium

Study Title:	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 <18 Years of Age with Chronic Kidney Disease and Hyperkalaemia (EMERALD)
Investigators and Study Centres:	Multicentre
Publications:	Warady BA, Gross C, Mayo M, Ma J, Yllana J, Shapiro L, et al. Patiromer treatment of hyperkalemia in adolescent children with CKD: initial results from EMERALD. Presented at the American Society of Nephrology Kidney Week. Washington (DC); Poster TH-PO764. J Am Soc Nephrol. 2019 Nov 5-10;30:317.
Studied Period:	6 July 2017 (first subject enrolled) to 13 May 2022 (study termination date)
Phase of Development:	2
Objectives:	Primary Objective: To assess change from baseline in serum potassium levels to Day 14 following administration of different doses of patiromer administered once daily (QD) in children 2 to <18 years of age with chronic kidney disease (CKD) and hyperkalaemia. Secondary Objective: To assess the safety and tolerability of patiromer in children 2 to <18 years of age with CKD and hyperkalaemia.
Methodology:	This was an open-label, multiple dose study in children and adolescents 2 to <18 years of age 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 for a total study participation duration for individual subjects of up to 28 weeks. The overall design of the study is presented schematically below:
Number of Subjects:	Planned: A minimum of 36 subjects (up to 54) for Cohorts 1 to 3. Enrolled: 23 subjects overall: • 14 subjects enrolled (a minimum of 12 subjects planned) in Cohort 1 (12 to <18 years of age) • 9 subjects enrolled (a minimum of 12 subjects planned) in Cohort 2 (6 to <12 years of age) • 0 subjects enrolled (a minimum of 12 subjects planned) in Cohort 3 (2 to <6 years of age) Analysed: • Safety population: 23 subjects

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	• Efficacy population: 23 subjects
Duration of Treatment:	Individual subject participation was up to 28 weeks including: 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.
Reference Therapy:	Not applicable
Criteria for Evaluation:	Primary Efficacy: • Change in serum potassium levels from baseline to Day 14 Secondary Efficacy: • 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) • 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) Safety: • Incidence and severity of adverse events (AEs) • Changes from baseline in clinical laboratory values (haematology and serum chemistry including serum magnesium, serum calcium, serum phosphate and serum fluoride) • Changes from baseline in vital signs and electrocardiogram (ECG)
Statistical Methods:	This study enrolled 23 participants (14 subjects in Cohort 1 and 9 subjects in Cohort 2). All 23 participants received patiromer. The study was terminated before any subject was recruited into Cohort 3. The safety population included all subjects who have taken at least 1 dose of patiromer. The efficacy population included all subjects who have taken at least 1 dose of patiromer. The safety population and efficacy population are the same in this study; therefore, all analyses are displayed with 1 population, i.e., safety population. Changes in serum potassium over time were summarised by starting dose and age group using descriptive statistics. The proportion (number and percentage) of subjects with serum potassium levels in the range of 3.8 to 5.0 mEq/l was summarised by visit; the 95% confidence interval (CI) was presented. Safety variables consisted of all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory test results (including serum potassium, calcium, magnesium, phosphate, and fluoride), vital signs and ECG, and reasons for dosing interruption or discontinuation. In addition, prescribed patiromer dose and actual dose exposure over time were summarised. Although local laboratory serum potassium values are presented, all laboratory values used for efficacy and safety assessments were based on central laboratory results.

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Summary of Results:

Study enrolment was impacted by the COVID-19 pandemic and Investigators have provided feedback that no additional subjects were likely to present for enrolment at the sites, as Investigators had no more patients in their database meeting the inclusion/exclusion criteria.

The study was terminated on 13 May 2022 as per Sponsor decision and following consultation with the Regulatory Authorities (EMA and FDA) on the paediatric development plan (EMEA-001720-PIP01-14-M02). This study report presents the results for 23 paediatric study participants from Cohort 1 (12 to <18 years of age) and Cohort 2 (6 to <12 years of age).

Demographics and Baseline Characteristics:

- The study enrolled a total of 23 paediatric participants (all White):
  - Cohort 1 (12 to <18 years of age): 14 participants with mean (standard deviation (SD)) age of 14.5 (1.99) years.
  - Cohort 2 (6 to <12 years of age): 9 participants with mean (SD) age of 8.0 (2.00) years.
- In Cohort 1, 3/14 participants were female (21.4%). In Cohort 2, 6/9 participants were female (66.7%).
- Participants enrolled were representative of the paediatric population of CKD patients with hyperkalaemia. In Cohort 1, the median eGFR at baseline was 27.0 ml/min/1.73 m^2 (interquartile range (IQR) 18.0, 38.0). In Cohort 2, the median eGFR at baseline was 26.0 ml/min/1.73 m^2 (IQR 22.0, 34.0). Mean (SD) serum potassium levels at baseline were 5.54 (0.323) mEq/l for Cohort 1 and 5.59 (0.439) mEq/l for Cohort 2.
- At baseline, mean (SD) body weight was 50.74 (12.31) kg (Cohort 1) and 24.40 (6.9) kg (Cohort 2).

Primary Efficacy

- The primary efficacy endpoint analysis of this study established that by Day 14, potassium levels decreased from baseline in both cohorts; mean (SD) potassium change from baseline was -0.50 (0.542) mEq/l in Cohort 1 (12 to <18 years of age) and -0.14 (0.553) mEq/l in Cohort 2 (6 to <12 years of age).

Secondary Efficacy

- The secondary efficacy endpoint analysis established that by Day 14, about 36.4% of subjects overall achieved serum potassium levels within the target range of 3.8 to 5.0 mEq/l; 50.0% of subjects in Cohort 1 and 12.5% in Cohort 2. Overall, the proportion of subjects with potassium values in the target range generally increased after Day 14 and while on treatment. At Week 26, 81.8% and 22.2% of subjects in Cohort 1 and Cohort 2, respectively, had serum potassium in the target range.
- Overall, reductions in serum potassium level were achieved and maintained, and due to dose adjustments after the 2-week PD/dose finding period further improved, throughout the study in both cohorts while on treatment. 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.

Dose to Response

- In Cohort 1, at Day 14 and at end of treatment, the median prescribed patiromer dose was 4.2 and 8.4 g/day, and the mean change from baseline in potassium was -0.50 (0.542) and -1.08 (0.736) mEq/l, respectively. In Cohort 2, at Day 14 and at end of treatment, the median prescribed patiromer dose was 6.0 and 8.0 g/day, and the mean change from baseline in potassium was -0.14 (0.553) and -0.50 (1.020) mEq/l, respectively. A higher dose of patiromer was associated with a larger reduction in serum potassium in a treatment interval.

Safety:

Overall Exposure

- In Cohort 1 (12 to <18 years of age), the minimum actual prescribed dose was 0.0 g/day, and the maximum dose was 25.2 g/day.
- In Cohort 2 (6 to <12 years of age), the minimum actual prescribed dose was 2.0 g/day, and the maximum dose was 12.0 g/day.

Adverse Events

- At least 1 TEAE was reported for 10/14 (71.4%) and 5/9 (55.6%) subjects in Cohort 1 and Cohort 2, respectively.
- Most of the TEAEs were mild (reported for 5/23 (21.7%) subjects overall) to moderate (9/23 (39.1%) subjects overall). One severe TEAE was reported for 1 subject in Cohort 1 (he experienced severe but non-serious TEAE of renal impairment, which was not resolved at the end of study and was assessed by the Investigator as not related to patiromer).
- Treatment-related TEAEs were reported in 4/23 subjects overall; in 2 of these subjects, the events belonged to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of Gastrointestinal (GI) Disorders. These were all non-serious events, mild to moderate in severity and there were no reported serious TEAEs related to study drug.
- TEAEs of mild hypokalaemia were reported for 1 subject in each cohort.
- A TEAE of moderate blood calcium decreased was reported for 1 subject in the study overall; a TEAE of mild blood calcium increased was reported for 1 subject in the study overall.
- There were no serious TEAEs reported and no TEAEs leading to patiromer discontinuation and/or study withdrawal.
- There were no deaths reported in this study.
- 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 treatment-related TEAEs were observed in the maximum dose treatment.

Clinical Laboratory and Other Safety Findings

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	• No laboratory values were reported as serious TEAEs, nor did any lead to drug discontinuation and/or withdrawal from study. • No subjects in the study had serum potassium levels <3.0 mEq/l; 1 subject had serum potassium <3.5 mEq/l, and another 2 subjects had an incidence of serum potassium <3.8 mEq/l. • No subjects in the study had serum magnesium levels <1.4 mg/dl. • No subjects in the study had serum calcium ≥12.0 mg/dl. For a single subject in the study (Cohort 1) a serum calcium value >11.0 mg/dl was reported (Week 26). Serum calcium values >10.2 mg/dl were reported for 3/23 subjects at baseline, for 1/22 subjects at Day 14, and for 5/21 subjects at Week 26. • No changes in serum phosphate or serum fluoride were reported as TEAE. • There were no significant effects on vital signs or physical examination findings. • No potassium-related ECG changes were reported at any visit for any subject. • No TEAEs related to phosphate or fluoride were reported.
Conclusions:	• The enrolled subjects are representative of patients with hyperkalaemia due to CKD 6 to <18 years of age and data are sufficient to support assessment of the PD effects, safety, and tolerability of patiromer in this population. • Patiromer is effective in treating hyperkalaemia in paediatric (6 to <18 years of age) CKD patients. • Treatment with different doses of patiromer for 26 weeks was safe and well tolerated in paediatric participants, 6 to <18 years of age.
Final Report Date:	30 September 2022