SYNOPSIS

Study Title:	VERIFIE (Velphoro Evaluation of Real-lIfe saFety, effectIveness and adherencE): Non-interventional study to investigate the short- and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis. Final analysis (36 months) Date: 20 November 2019 Authors: Dr. Manuela Stauss-Grabo (Fresenius Medical Care Deutschland GmbH), Dr. Sebastian Walpen (Vifor Fresenius Medical Care Renal Pharma)
Keywords:	Hyperphosphataemia, phosphate binder, dialysis, sucroferric oxyhydroxide, chronic kidney disease
Rationale and Background:	Hyperphosphataemia is a common complication in patients with advanced chronic kidney disease (CKD) undergoing dialysis. Since excess phosphate cannot easily be removed by dialysis and dietetic restrictions are often not sufficient, oral phosphate binders (PBs) are required to control serum phosphorus (sP) levels. The new oral highly potent PB Velphoro has been approved by the FDA (November 2013) and by the EMA (August 2014).
Research Questions and Objectives:	Primary Objective(s): • To evaluate short- and long-term (beyond 1 year) safety and tolerability of Velphoro in general in HD and PD patients. • To specifically assess the potential risk of iron accumulation of Velphoro in HD and PD patients. • To investigate the potential masking of GI bleedings in patients treated with Velphoro in HD and PD patients. Secondary Objective(s): • To evaluate the effectiveness of Velphoro in routine clinical practice. • To evaluate adherence to Velphoro therapy.
Study Design:	Non-interventional, prospective, multicentre, multinational (European), cohort study.
Setting:	The study has been conducted in 178 sites in 7 countries. The total documentation period for this final analysis was 6 April 2016 to 6 April 2019.
Subjects and Study Size, Including Drop-outs:	Planned total number of patients: 1,000. A total of 1,452 patients were screened and 1,406 patients were enrolled into the study. Of the enrolled patients, 1,365 patients are included in the safety analysis set (SAF) and 1,322 patients are included in the full analysis set (FAS). In total, 682 of 1,365 patients in the SAF (49.96%) and 650 of 1,322 patients in the FAS (49.17%) withdrew or prematurely discontinued the study. The most commonly reported primary reasons for premature discontinuations were permanent discontinuation of Velphoro treatment, adverse drug reactions

	(ADRs)/medical events of special interest (MESIs), and death.
Variables and Data Sources:	Medical records, routine measurements and assessments (e.g., laboratory parameters), patient questionnaires.
Results:	**Population Characteristics** Approximately two-thirds of all patients were male (SAF: 66.52%, FAS: 66.04%). The mean (standard deviation (SD)) age at date of informed consent was 61.5 (14.94) years in the SAF and 61.4 (14.96) years in the FAS. At baseline, more than half of patients received HD, and about one-third of patients received haemodiafiltration (HDF). The remaining 12% of patients were undergoing PD. Before start of Velphoro treatment, 850 patients (62.27%) in the SAF had been treated with PBs other than Velphoro and 618 patients (45.27%) were concomitantly treated with PBs other than Velphoro during the study conduct. **Exposure to Velphoro** In the SAF, the mean (SD) daily dose of Velphoro at baseline was 1,047.2 (486.34) mg and the last documented mean daily dose of Velphoro was 1,204.6 (618.49) mg, while the mean daily dose of Velphoro during the observation period was 1,172.7 (539.91) mg. The average duration of exposure to Velphoro, excluding off-days, was almost as long as the average duration of therapy with Velphoro, including off-days both exceeding 1 year in length (58.3 weeks compared to 59.3 weeks in the SAF, respectively). During the observation period, a total of 507 of the 1,365 patients (37.14%) permanently discontinued Velphoro treatment, with more than half of the discontinuations due to ADRs/toxicity/MESIs/fatal events. **Primary Objectives: Safety of Velphoro** All safety analyses are presented for the SAF. A total of 531 patients (38.90%; exposure adjusted incidence rate (EAIR) per year: 0.461) reported at least 1 ADR. The Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) with the highest incidences were diarrhoea (194 patients (14.21%); EAIR per year: 0.133) and faeces discoloured (128 patients (9.38%); EAIR per year: 0.090). Serious adverse drug reactions (SADRs) were reported for 26 patients (1.90%; EAIR per year: 0.017). A total of 250 patients (18.32%, EAIR per year: 0.176) reported at least 1 MESI. Most often MESIs affected the MedDRA system organ class (SOC) of GI Disorders (249 patients, 18.24%; EAIR per year: 0.175). Two patients had MESIs indicative of iron accumulation (iron overload) during the observation period. MESIs of diarrhoea were reported for 217 patients (15.90%; EAIR per year: 0.151). Regarding GI bleeding, the most frequently reported event was GI haemorrhage (18 patients, 1.32%; EAIR per year: 0.012). MESIs were serious in 13 patients who had diarrhoea and in most patients who had GI disorders other than diarrhoea, resulting in a total of 49 patients (3.59%) who had serious MESIs. The corresponding EAIR was 0.032 per year (95% confidence interval (CI): 0.023, 0.042). MESIs considered as related to Velphoro treatment were reported for 197 patients (14.43%); the corresponding EAIR was 0.135 per year. When evaluating the patients with related MESIs by category, 178 patients

	(71.20%) had a causality assessment of "yes", and 18 patients (7.20%) had a causality assessment of "not assessable". For a total of 194 of 217 patients with diarrhoea, 2 of 18 patients with GI haemorrhage, 1 of 4 patients with haematemesis, 1 of 6 patients with rectal haemorrhage, and 1 of 2 patients with iron overload the events were considered related to Velphoro treatment. MESIs that were not assessable, or for which the causality assessment was missing included diarrhoea in 22 patients, GI haemorrhage in 1 patient, and haematemesis in 1 patient. The incidence of non-related MESIs was 4.98% (68 patients) and the EAIR was 0.045 per year. A total of 119 patients (8.72%) died. The EAIR of fatal events was 0.076 per year. The majority of the patients who died experienced events in the MedDRA SOC of Cardiac Disorders (44 patients, 3.22%), General Disorders and Administration Site Conditions (32 patients, 2.34%), and Infections and Infestations (17 patients, 1.25%). The fatal event death (MedDRA PT) occurred in 17 patients (1.25%) and cardiac arrest (MedDRA PT) was reported for 14 patients (1.03%). Overall, 1,144 ADRs, MESIs, and fatal events were reported during the observation period: 38 ADRs and 59 MESIs were serious. Most events were of mild severity (520 events, 45.45%). Moderate and severe events were reported for about a fifth of patients each (243 events, 21.24% and 222 events, 19.41%, respectively). The majority of events (692 events, 60.49%) were considered related to Velphoro treatment, while 245 events (21.42%) were considered not related. For 194 of 217 patients with diarrhoea, the reported diarrhoea was assessed as related to Velphoro; for 7 patients the events were both serious and related. The most frequent time to first diarrhoea was 1 week or less, reported for 39 of 217 patients. Up to 6 months after the start of treatment with Velphoro, there was a clear trend for the number of patients experiencing their first diarrhoea to decrease steadily over time, and after 6 months the number of patients experiencing their first diarrhoea appeared to continue in a steady state of 5-8 patients per month. The severity of first diarrhoea showed no obvious temporal trend. Diarrhoea was reported as resolved or as resolved with sequelae in 186 patients. For two-thirds of patients (123 patients, 66.13%), the first event of diarrhoea resolved with or without sequelae within 2 weeks of onset. A duration of diarrhoea of >7 weeks was reported for 20 patients (10.75%). The distribution of events by severity did not appear to vary with event duration. The proportion of stool changes since the preceding visit continually decreased from baseline to end of observation. The proportion of stool changes classified as diarrhoea increased progressively from Month 1 (20.76%) to Month 12 (37.84%). Mean ferritin concentrations were observed to increase with time. The trend was most apparent between baseline and Month 12. Mean (SD) ferritin concentrations were 377.26 (326.421) ng/ml at baseline, 368.46 (285.407) ng/ml at Month 1, 391.68 (298.745) ng/ml at Month 3, 406.43 (333.925) ng/ml at Month 6, 419.44 (308.696) ng/ml at Month 12, and 420.90 (290.184) ng/ml at Month 18. At the last completed visit, mean (SD) ferritin concentrations were 413.72 (303.932) ng/ml. Mean transferrin concentrations slightly decreased from baseline to Month 12. Mean transferrin saturation (TSAT) concentrations remained relatively constant during the observation period. None of these

changes were considered clinically relevant. It is important to note that more than half of patients (64.47%) were treated with concomitant intravenous (IV)/oral iron which needs to be considered when interpreting these results.

A total of 38 patients had concomitant GI bleedings. Most of these patients had 1 concomitant GI bleeding (32 patients, 2.34%). The remaining patients had 2 concomitant GI bleedings (5 patients, 0.37%), and 4 concomitant GI bleedings (1 patient, 0.07%). Time from Velphoro treatment start to first GI bleeding was highly variable, exceeding 12 months for 13 of 38 patients (34.21%), with a median time of 224.5 days (range: 15 days to 818 days). Most of the patients (32 patients, 84.21%) had specific risks for GI bleedings at or after Velphoro treatment start including medication (24 patients, 63.16%), history of GI bleeding (10 patients, 26.32%), medical conditions/disease (7 patients, 18.42%), and other (blood thinner) (2 patients, 5.26%). The most common signs and symptoms for diagnosis of GI bleeding were: haemoglobin (Hb) drop: Hb value at diagnosis (15 patients, 39.47%), macroscopically visible red blood passed from the rectum (either in toilet bowl, on toilet paper, streaks on faeces) (9 patients, 23.68%), blackened and tarry stools, patient reports unusual weakness/tiredness/dizziness (7 patients each, 18.42%), unexplained hypotension or shock, blackened stools of normal consistency (6 patients each, 15.79%), haematemesis, and Hb drop: Hb value prior to bleeding (4 patients each, 10.53%).

A documented GI bleeding report was available for 40 GI bleedings. For most of these (36 bleedings, 90%), no delay in GI bleeding diagnosis caused by Velphoro-related stool discolouration was reported. For the remaining 4 bleedings (10%), Velphoro-related stool discolouration was reported as causing an insignificant delay in the diagnosis of GI bleeding, without affecting patient health. All but 1 of the 40 bleedings were considered not related to Velphoro treatment. For all 38 patients, the documented GI bleedings were serious MESIs.

Secondary Objective

One of the secondary objectives of the study is to evaluate the effectiveness of Velphoro in routine clinical practice.

Evaluations were based on sP values. The mean (SD) value of sP at baseline was 6.28 (1.565) mg/dl. Mean sP values showed a clear trend to decrease with time, up to Month 30. The rate of decrease was highest in the early months, particularly between baseline and Month 1, and gradually reduced thereafter, reaching 5.71 (1.601) mg/dl by Month 1 and 5.26 (1.826) mg/dl by Month 30. With the last observation carried forward (LOCF) analysis, similar trends were observed for both the absolute and relative changes in sP values.

The other secondary objective of the study is to evaluate the adherence to Velphoro therapy. The evaluation of adherence is based on patient reported outcomes (PROs).

No clear and consistent change with regards to food intake or appetite compared to baseline were seen during the study.

At baseline (Velphoro treatment start), information regarding previous PBs other than Velphoro was collected with the mean (SD) accumulated daily drug intake (number of pills) of 3.6 (2.79) pills (median: 3.0 pills). During Velphoro treatment, this number was equal to 2.3 (1.30) pills at Month 1 and 2.5 (1.70) pills at Month 3 (median 2.0 pills). Thereafter, it slightly increased again

	reaching a mean of 3.0 (1.85) pills (median: 3.0) at Month 30. With regard to drug adherence based on the Morisky questionnaire, the most frequent score category at all visits up to Month 12 was 4: very adherent in more than 43% of patients. The percentage of very adherent patients was 43.52% at baseline, increased to 55.64% at Month 1, decreased again to 47.42% at Month 3, and remained roughly constant at the remaining time points (Month 6: 46.53%, Month 12: 47.35%). Less than 15% of patient at all visits had a score of 0-1: not adherent at all. At baseline, 14.70% of patients were “not adherent at all”; this percentage decreased to 8.14% at Month 1 and increased to 12.89% at Month 3, 12.24% at Month 6, and decreased slightly again to 10.60% at Month 12. The mean and the median of the compliance score based on the AIDS Clinical Trials Group (ACTG) questionnaire at Month 1, Month 3, Month 6, and Month 12 were constant throughout. The low patient numbers at later follow-up visits needs to be considered when interpreting the results. The previous PB was most frequently administered by swallowing tablets or pills with water (191 of 347 patients, 55.04%). With regard to the number of tablets/pills/capsules of the previous PB per day, most frequently patients took 0-3 tablets/pills/capsules per day (133 patients, 38.33%), followed by >3 to 6 tablets/pills/capsules per day (90 patients, 25.94%). The mean convenience score based on the adapted Treatment Satisfaction Questionnaire for Medication (TSQM)-9 algorithm (score from 0 (least convenient) to 100 (most convenient)) was around 70 (median: 75.0) from baseline to Month 24. Thereafter, it decreased to a mean (SD) of 62.9 (16.94) and median 66.7 at Month 30. When interpreting this, however, the low number of patients at Month 30 (33 patients) has to be taken into account. Similar values were seen for treatment-naïve patients. During the observation period, most patients were not hospitalised (866 patients, 63.44%), while 292 patients (21.39%) in the SAF were hospitalised once, 89 patients (6.52%) were hospitalised twice, and the remaining patients were hospitalised between 3 and 9 times, with the exception of 1 patient (0.07%) who was hospitalised 17 times. The total number of hospitalisations was 991. In 8.78% of all hospitalisations, the primary reasons for hospitalisation were ADRs, MESIs, or fatal events. A total of 16.95% of hospitalisations were pre-planned; 28.25% were not associated with an ADR. No relevant changes in body weight/body mass index (BMI) were observed during the observation period. Slight decreases from baseline in systolic blood pressure and diastolic blood pressure were observed at nearly all visits up to Month 24. The following laboratory parameters were analysed: serum calcium, Hb, intact parathyroid hormone, serum sodium, serum potassium, thyroid-stimulating hormone (TSH), alkaline phosphatase, albumin, 25-hydroxy Vitamin D, C-reactive protein (CRP), normalised protein catabolic rate (nPCR), creatinine, and urea. Most changes in laboratory values during the observation period were not relevant. Serum potassium concentrations showed a clear reduction between baseline and Month 6. An increase in alkaline phosphatase and CRP levels was observed over time. Urea levels showed a trend to decrease between baseline and Month 12. Values of all other laboratory parameters remained constant or showed no consistent trends over time.

Discussion:	Based on this final analysis and considering the limitations of this Non-interventional Study (NIS), the benefit/risk profile of Velphoro remains as it is: there were no unexpected findings and no new safety concerns. The safety profile was within the expectations and in line with clinical data from the Phase 3 studies PA-CL-05A/05B. The occurrence of diarrhoea (onset, severity, and duration) is in line with the observations from the Phase 3 studies PA-CL-05A/05B: first events of diarrhoea were predominantly of mild intensity and occurred early after Velphoro treatment start. Small increases in serum ferritin compared with baseline are in line with the observation from the Phase 3 studies PA-CL-05A/05B. The current available information does not support a change of the safety profile in terms of potential iron accumulation. The number of reported GI bleedings was low with none of these having a clinically significant delay in GI bleeding diagnosis. Velphoro-related stool discolouration was reported as causing an insignificant delay in the diagnosis of GI bleeding in a small number of patients, without affecting patient health. The effectiveness parameter (sP) clearly showed that Velphoro is able to reduce sP in a real-life setting consistent with the Phase 3 studies PA-CL-05A/05B.
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