Renal Replacement Therapy

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Effects of ferric citrate hydrate in patients with chronic kidney disease and heart failure: subgroup analysis of a long-term, real-world, post-marketing surveillance study

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Abstract

Background: Iron deficiency is widely present in patients with heart failure (HF) and is associated with an increased risk of mortality and poor clinical outcomes regardless of anemia. HF is highly prevalent in patients with chronic kidney disease (CKD). However, existing oral iron preparations have failed to improve iron-related parameters in patients with HF, and intravenous iron preparations are recommended. Ferric citrate hydrate (FC) is an oral iron-based phosphate binder for CKD that is also approved for the treatment of patients with iron-deficiency anemia in Japan. In this subgroup analysis, we evaluated the effect of oral FC on iron-related parameters in CKD patients with and without HF.

Methods: We examined iron- and phosphate-related parameters and adverse drug reactions in subpopulations of CKD patients with and without HF enrolled in a previously reported 104-week, real-world, post-marketing surveillance study of FC in Japan.

Results: Among 2811 enrolled CKD patients, 348 patients had HF and 2352 did not have HF, including 166 and 1401 undergoing hemodialysis (HD), 36 and 173 undergoing peritoneal dialysis (PD), and 146 and 778 non-dialysis-dependent (ND) patients, respectively. The mean changes (95% confidence interval (CI)) in serum ferritin from baseline to week 36 were 90.98 (62.99–118.97) and 81.86 (72.68–91.03) ng/mL in HD, 158.64 (108.91–208.36) and 132.91 (98.59–167.23) ng/mL in PD, and 68.06 (40.40–95.73) and 99.75 (81.10–118.40) ng/mL in ND group, respectively. The mean changes (95% CI) in transferrin saturation (TSAT) (%) from baseline to week 12 in patients with and without HF were 12.79 (9.15–16.44) % and 9.57 (8.46–10.68) % in HD, 9.55 (1.31–17.78) % and 4.96 (1.44–8.48) % in PD, and 5.85 (2.02–9.69) % and 5.21 (3.34–7.09) in ND patients, respectively. Levels of these parameters were well maintained thereafter. Mean serum phosphate levels decreased after FC treatment initiation and were well maintained in all groups.

Conclusions: This study demonstrated that oral FC had a tendency to increase serum ferritin and TSAT, and controlled serum phosphate in CKD patients regardless of the presence of HF.

Trial registration This surveillance was conducted in accordance with the Good Post-marketing Study Practice of Ministry of Health, Labour, and Welfare in Japan.

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Keywords: Ferric citrate hydrate, Heart failure, Oral iron preparation, Iron-deficiency anemia, Transferrin saturation, Serum ferritin

Background

Patients with heart failure (HF) often have iron deficiency with or without anemia [1, 2]. Previous studies showed a high prevalence of these conditions in patients with acute and chronic HF. Iron deficiency, defined as ferritin < 100 ng/mL or 100–299 ng/mL with transferrin saturation (TSAT) < 20%, was found in 50% of patients with chronic HF [3] and 69–75% of patients with acute HF [4], whereas anemia (defined by the World Health Organization as hemoglobin < 13 g/dL in men and < 12 g/dL in women) was found in 30% of patients with advanced HF [5] and 57–58% of patients with chronic or acute HF [6, 7]. Anemia and iron deficiency are associated with mortality and poor outcomes in HF patients with reduced or preserved left ventricular ejection fraction (HFrEF or HFpEF) [3, 5–8]. The 2021 European Society of Cardiology (ESC) guidelines recommend periodical screening for anemia and iron deficiency, and the use of intravenous iron preparations with ferric carboxymaltose to treat this condition [1]. Intravenous iron was shown to increase iron-related parameters and improve the exercise capacity and quality of life of patients with chronic HF [9, 10] and to reduce the risk of re-hospitalization in patients who have recovered from acute HF [11]. However, there is currently no evidence to indicate that oral iron preparations can improve outcomes in patients with HF. In the IRONOUT HF randomized trial, oral iron (iron polysaccharide, 150 mg, twice daily for 16 weeks) failed to increase iron absorption (median changes (95% confidence interval (CI)) of serum ferritin and TSAT after 16 weeks of treatment were 18 (− 8 to 38) ng/mL and 2 (− 3 to 7) %, respectively) or improve the exercise capacity or quality of life of patients with HFrEF and iron deficiency [12]. In another randomized study, the erythropoiesis-stimulating agent (ESA) darbepoetin alfa failed to improve mortality and increased the risks of embolic and thrombotic events in patients with systolic HF and mild-to-moderate anemia [13]. ESC guidelines accordingly do not recommend the use of ESAs to treat anemia in patients with HF, and the Japanese Circulation Society guidelines for the treatment of HF state that there is currently no established evidence on how to treat anemia in patients with acute and chronic HF [14, 15].

Ferric citrate hydrate (FC; Riona®; Torii Pharmaceutical Co., Ltd., Tokyo, Japan) has been approved in Japan as an oral iron-based phosphate binder that effectively controls serum phosphate concentrations in patients with chronic kidney disease (CKD), including dialysis- and non-dialysis-dependent patients [16–18]. Furthermore, FC increased hemoglobin levels in patients with iron-deficiency anemia with or without CKD [19, 20] and has been approved to treat iron-deficiency anemia in Japan. Ferric citrate (Auryxia®; Akebia Therapeutics, Inc., Cambridge, MA, USA) has the same active ingredient as that of Riona® although the formulation provides different amounts of elemental iron (Riona® has approximately 60 mg elemental iron per 250 mg tablet, whereas Auryxia® has 210 mg elemental iron per 1 g tablet), and it has been approved to treat hyperphosphatemia in patients with dialysis-dependent CKD and iron-deficiency anemia in patients with non-dialysis-dependent CKD in the USA [21, 22]. A previous post hoc analysis compared the iron-related parameters of ferric citrate (Auryxia®) in non-dialysis-dependent patients with CKD and iron-deficiency anemia with or without HF from phase 2 and 3 trials in the USA. They found mean (standard deviation (SD)) increases from baseline to week 12 in serum ferritin of 201.6 (172.3) pmol/L [89.7 (76.7) ng/mL] and TSAT of 10.9 (13.7) % in patients with HF, which were comparable with changes in patients without HF. However, the previous analysis was conducted only in non-dialysis-dependent patients with CKD and iron-deficiency anemia, and the mean ferric citrate (Auryxia®) dose was 5000 mg/day (1050 mg iron/day) [23]. The dose of ferric citrate (Auryxia®) provided a higher dose of elemental iron than the dose used in the IRONOUT HF randomized trial, oral iron polysaccharide (150 mg, twice daily, 300 mg iron/day) [12].

We previously conducted a 104-week, real-world, post-marketing surveillance study of FC in dialysis- and non-dialysis-dependent patients with CKD [24] and showed that FC improved iron-related parameters, with no new safety concerns. In the current study, we analyzed the association of FC on iron- and erythrocyte-related parameters, and CKD-mineral and bone disorder (MBD)-related parameters in CKD patients with and without HF using data from this previous post-marketing surveillance study [24]. The study population was expected to include a large subpopulation of patients with HF, given that CKD and HF frequently coexist [1] and the prevalence of CKD in patients with HF in Japan was reported to be 23% [25].

Methods

Study design

This post-marketing surveillance study was conducted in Japan as part of a risk management plan to ensure the long-term safety of a newly approved drug in a real-world

setting. Patients were registered centrally from January 30, 2015. Case report forms were collected from participating institutions for up to a maximum of 2 years. Data collection was terminated on April 30, 2020 [24].

Patients

Patients included in the surveillance study have been described in detail in a previous report [24]. Briefly, CKD patients, including patients undergoing hemodialysis (HD group), peritoneal dialysis (PD group), or no dialysis (ND group), were registered within 14 days from the initiation of FC treatment and followed up prospectively. Patients undergoing combined dialysis (HD plus PD) were excluded from the analyses. Among these registered patients, patients diagnosed with comorbid HF by a physician at baseline were defined as patients with HF, and the other patients were defined as patients without HF in the current analyses. All patients whose case report forms were returned at least once after their first visit were analyzed for safety (safety-analysis set) and patients within this set with available effectiveness data were analyzed for effectiveness (effectiveness-analysis set).

FC treatment

FC (250 mg tablet containing approximately 60 mg of elemental ferric iron) was administered orally three times per day immediately after a meal. The starting dose was 500 mg (1500 mg/day) as recommended in the package insert. The dose was adjusted by physicians according to serum phosphate concentrations or clinical status, with a maximum allowed dose of 6000 mg/day. Concomitant medications (e.g., phosphate binders and iron preparations) were allowed [24].

Evaluation of iron- and erythrocyte-related parameters

Iron- and erythrocyte-related parameters, including serum ferritin, serum iron, TSAT, and hemoglobin, were measured as parameters of special interest in the safety-analysis set at baseline, 4, 12, 16, 24, 28, 36, 52, 76, and 104 weeks after the initiation of FC treatment, and at discontinuation of the treatment. The absolute value of each parameter and the difference from baseline were summarized in each group using descriptive statistics. Time-course changes in serum ferritin, and TSAT were plotted for each group throughout the observation period.

Evaluation of CKD-MBD-related parameters

CKD-MBD-related parameters, including serum phosphate, serum calcium, and intact parathyroid hormone, were measured in the effectiveness-analysis set at baseline, 4, 12, 16, 24, 28, 36, 52, 76, and 104 weeks after the initiation of FC treatment, and at treatment discontinuation. Serum calcium was corrected when serum albumin was < 4.0 g/dL using the formula: corrected calcium [mg/dL] = (absolute value of serum calcium [mg/dL]) + [4 − (serum albumin [g/dL])]. When serum albumin was ≥ 4.0 g/dL, corrected calcium was equal to the absolute serum calcium value. The absolute value of each parameter and the difference from baseline were summarized in each group using descriptive statistics. Time-course changes in serum phosphate were plotted for each group throughout the observation period.

Adverse drug reactions

Adverse drug reactions were recorded in the safety-analysis set using preferred terms from MedDRA Ver. 23.0 and were summarized using descriptive statistics. If a patient experienced an event multiple times, it was recorded as one event.

Statistical analysis

Patient characteristics, iron- and erythrocyte-related parameters and adverse drug reactions were analyzed in the safety-analysis set, and CKD-MBD-related parameters were analyzed in the effectiveness-analysis set. On the basis of data from all Japanese pre-approval clinical studies, we planned to enroll 1000 patients in the HD group, 100 in the PD group, and 500 in the ND group in the post-marketing surveillance study to evaluate long-term safety in the entire CKD population [24]. The current study used the same data set. Mean changes from baseline to each time point and the 95% CI were analyzed for serum ferritin and TSAT at 12, 36, 52, and 104 weeks. All statistical analyses were performed using SAS Ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

In this observational post-marketing surveillance study, 2811 patients with CKD were registered from 573 institutions [24]. Patients whose case report forms were not returned ($n = 76$) or who underwent combined dialysis (HD and PD) or did not return after the first visit or did not meet registration criteria were excluded. Among the remaining patients, patients with and without comorbid HF were analyzed in this study (safety-analysis set, $n = 348$ and $n = 2352$), comprising 166 and 1401 patients in the HD group, 36 and 173 patients in the PD group, and 146 and 778 patients in the ND group, respectively. The effectiveness-analysis set ($n = 303$ and $n = 2041$) comprised 146 and 1232 patients in the HD group, 33 and 150 patients in the PD group, and 124 and 659 patients in

the ND group, after excluding 45 and 309 patients from the safety-analysis set, respectively (Fig. 1).

Patients with and without comorbid HF characteristics are summarized in Table 1. The mean (standard deviation; SD) age of patients with and without comorbid HF was 68.3 (12.3) and 65.3 (12.7) years in the HD group, 66.4 (13.0) and 62.7 (12.6) years in the PD group, and 68.4 (14.2) and 65.7 (13.5) years in the ND group, respectively. There were more male than female patients in all groups. At baseline, the use of iron preparations (oral or intravenous) in patients with and without comorbid HF was 48/166 patients (28.9%) and 361/1401 patients (25.8%) in the HD group, 3/36 patients (8.3%) and 15/173 patients (8.7%) in the PD group and 12/146 patients (8.2%) and 68/778 patients (8.7%) in the ND group, respectively.

The daily mean (SD) dose of FC during the study in patients with and without comorbid HF was 1054.5 (516.3) mg and 1082.6 (510.7) mg in the HD group, 951.0 (456.6) mg and 976.4 (509.0) mg in the PD group, and 896.9 (524.1) mg and 845.5 (417.3) in the ND group, respectively.

Iron- and erythrocyte-related parameters

Median (interquartile range (IQR): first quartile, third quartile) serum ferritin levels in patients with and

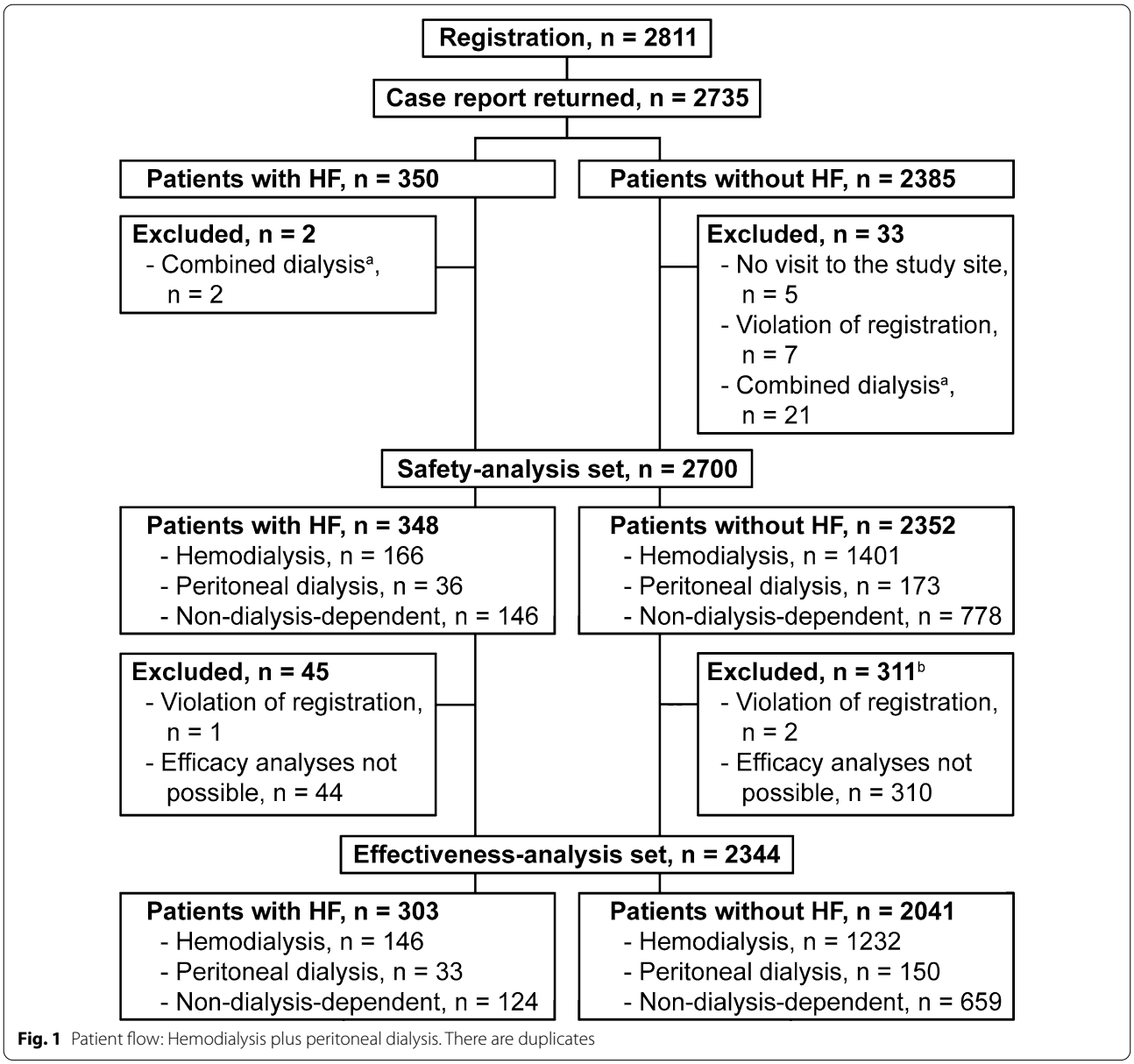

Fig. 1 Patient flow: Hemodialysis plus peritoneal dialysis. There are duplicates

Table 1 Patient characteristics (safety-analysis set)

Characteristic, *n* (%) unless otherwise noted	Patients with heart failure			Patients without heart failure		
	HD, *n* = 166	PD, *n* = 36	ND, *n* = 146	HD, *n* = 1401	PD, *n* = 173	ND, *n* = 778
Sex						
Male	102 (61.45)	29 (80.56)	93 (63.70)	890 (63.53)	113 (65.32)	400 (51.41)
Female	64 (38.55)	7 (19.44)	53 (36.30)	511 (36.47)	60 (34.68)	378 (48.59)
Age [years], mean ± standard deviation						
	68.3 ± 12.3	66.4 ± 13.0	68.4 ± 14.2	65.3 ± 12.7	62.7 ± 12.6	65.7 ± 13.5
Hospital visit						
Inpatient	10 (6.02)	5 (13.89)	18 (12.33)	29 (2.07)	15 (8.67)	47 (6.04)
Outpatient	156 (93.98)	31 (86.11)	128 (87.67)	1372 (97.93)	158 (91.33)	731 (93.96)
Primary cause of kidney failure[a]						
Diabetic nephropathy	72 (43.37)	19 (52.78)	78 (53.42)	578 (41.26)	61 (35.26)	299 (38.43)
Chronic glomerulonephritis[b]	31 (18.67)	7 (19.44)	14 (9.59)	362 (25.84)	52 (30.06)	164 (21.08)
Nephrosclerosis	33 (19.88)	9 (25.00)	42 (28.77)	210 (14.99)	39 (22.54)	155 (19.92)
Polycystic kidney	2 (1.20)	0 (0.00)	7 (4.79)	62 (4.43)	6 (3.47)	48 (6.17)
Unknown	19 (11.45)	2 (5.56)	7 (4.79)	149 (10.64)	13 (7.51)	92 (11.83)
Others	15 (9.04)	0 (0.00)	10 (6.85)	85 (6.07)	6 (3.47)	60 (7.71)
Dialysis vintage [year]						
< 0.5	20 (12.05)	8 (22.22)	0 (0.00)	147 (10.49)	37 (21.39)	0 (0.00)
0.5 to < 1	19 (11.45)	3 (8.33)	0 (0.00)	173 (12.35)	29 (16.76)	0 (0.00)
1 to < 3	31 (18.67)	17 (47.22)	0 (0.00)	275 (19.63)	50 (28.90)	0 (0.00)
3 to < 5	23 (13.86)	3 (8.33)	0 (0.00)	191 (13.63)	37 (21.39)	0 (0.00)
5 to < 10	37 (22.29)	5 (13.89)	0 (0.00)	319 (22.77)	19 (10.98)	0 (0.00)
10 to < 20	23 (13.86)	0 (0.00)	0 (0.00)	219 (15.63)	1 (0.58)	0 (0.00)
≥ 20	12 (7.23)	0 (0.00)	0 (0.00)	77 (5.50)	0 (0.00)	0 (0.00)
Unknown	1 (0.60)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Never	0 (0.00)	0 (0.00)	146 (100.00)	0 (0.00)	0 (0.00)	778 (100.00)
Complications						
Cardiovascular disease	166 (100.00)	36 (100.00)	146 (100.00)	1133 (80.87)	156 (90.17)	706 (90.75)
No comorbidities other than cardiovascular disease	3 (1.81)	0 (0.00)	3 (2.05)	100 (7.14)	11 (6.36)	39 (5.01)
Comorbidities present in addition to cardiovascular disease	163 (98.19)	36 (100.00)	143 (97.95)	1298 (92.65)	162 (93.64)	739 (94.99)
Gastrointestinal disease	112 (67.47)	21 (58.33)	56 (38.36)	719 (51.32)	72 (41.62)	225 (28.92)
Hepatic disease	20 (12.05)	4 (11.11)	9 (6.16)	81 (5.78)	10 (5.78)	50 (6.43)
Metabolic disease	131 (78.92)	34 (94.44)	135 (92.47)	979 (69.88)	145 (83.82)	690 (88.69)
Other disease	155 (93.37)	36 (100.00)	133 (91.10)	1181 (84.30)	146 (84.39)	607 (78.02)
Concomitant medication						
No	0 (0.00)	0 (0.00)	1 (0.68)	4 (0.29)	0 (0.00)	8 (1.03)
Yes	166 (100.00)	36 (100.00)	145 (99.32)	1397 (99.71)	173 (100.00)	770 (98.97)
Hyperphosphatemia agent						
No	61 (36.75)	11 (30.56)	113 (77.40)	476 (33.98)	71 (41.04)	566 (72.75)
Yes	105 (63.25)	25 (69.44)	33 (22.60)	925 (66.02)	102 (58.96)	212 (27.25)
Hyperparathyroidism secondary agent						
No	29 (17.47)	6 (16.67)	90 (61.64)	268 (19.13)	35 (20.23)	407 (52.31)
Yes	137 (82.53)	30 (83.33)	56 (38.36)	1133 (80.87)	138 (79.77)	371 (47.69)
Erythropoiesis-stimulating agent						
No	17 (10.24)	1 (2.78)	23 (15.75)	100 (7.14)	3 (1.73)	102 (13.11)
Yes	149 (89.76)	35 (97.22)	123 (84.25)	1301 (92.86)	170 (98.27)	676 (86.89)
Gastric acid secretion inhibitor						
No	43 (25.90)	13 (36.11)	76 (52.05)	570 (40.69)	91 (52.60)	481 (61.83)

Table 1 (continued)

Characteristic, *n* (%) unless otherwise noted	Patients with heart failure			Patients without heart failure		
	HD, *n* = 166	PD, *n* = 36	ND, *n* = 146	HD, *n* = 1401	PD, *n* = 173	ND, *n* = 778
Yes	123 (74.10)	23 (63.89)	70 (47.95)	831 (59.31)	82 (47.40)	297 (38.17)
Iron preparation						
No	118 (71.08)	33 (91.67)	134 (91.78)	1040 (74.23)	158 (91.33)	710 (91.26)
Yes	48 (28.92)	3 (8.33)	12 (8.22)	361 (25.77)	15 (8.67)	68 (8.74)
Others						
No	7 (4.22)	2 (5.56)	4 (2.74)	132 (9.42)	26 (15.03)	65 (8.35)
Yes	159 (95.78)	34 (94.44)	142 (97.26)	1269 (90.58)	147 (84.97)	713 (91.65)
Dose of FC [mg/day], mean ± standard deviation						
	1054.5 ± 516.3	951.0 ± 456.6	896.9 ± 524.1	1082.6 ± 510.7	976.4 ± 509.0	845.5 ± 417.3

[a] Multiple answers possible

[b] Including IgA nephropathy

HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group; FC. Ferric citrate hydrate

without comorbid HF at baseline were 44.50 (23.70, 94.60) ng/mL and 44.50 (21.10, 88.10) ng/mL in the HD group, 146.00 (58.40, 223.60) ng/mL and 85.60 (51.00, 158.00) ng/mL in the PD group, and 91.00 (53.50, 122.30) and 80.65 (41.00, 154.40) in the ND group, respectively (Table 2). Median serum ferritin levels showed a gradually increasing trend in all groups until around 36 weeks after treatment initiation: the mean changes (95% CI) in serum ferritin in patients with and without comorbid HF from baseline to week 36 were 90.98 (62.99–118.97) ng/mL and 81.86 (72.68–91.03) ng/mL in the HD group, 158.64 (108.91–208.36) ng/mL and 132.91 (98.59–167.23) ng/mL in the PD group, and 68.06 (40.40–95.73) and 99.75 (81.10–118.40) ng/mL in the ND group, respectively. The levels became stable thereafter (Tables 2, 3 and Fig. 2).

Mean (SD) TSAT levels in patients with and without comorbid HF at baseline were 21.34 (13.30) % and 22.04 (11.95) % in the HD group, 28.47 (11.01) % and 30.76 (14.37) % in the PD group, and 23.26 (13.55) % and 28.55 (12.08) % in the ND group, respectively (Table 2), and these also showed an increasing trend until around 12 weeks after treatment initiation and then remained stable in all groups: mean changes (95% CI) in TSAT in patients with and without comorbid HF from baseline to week 12 were 12.79 (9.15–16.44) % and 9.57 (8.46–10.68) % in the HD group, 9.55 (1.31, 17.78) % and 4.96 (1.44, 8.48) % in the PD group, and 5.85 (2.02, 9.69) % and 5.21 (3.34, 7.09) % in the ND group, respectively (Table 2, Table 3 and Fig. 3). Hemoglobin levels were well controlled in all groups (Table 2).

CKD-MBD-related parameters

Mean (SD) serum phosphate levels in patients with and without comorbid HF at baseline were 6.73 (1.45) mg/dL and 6.56 (1.38) mg/dL in the HD group, 6.62 (1.36) mg/dL and 6.06 (1.35) mg/dL in the PD group, and 5.33 (1.09) mg/dL and 5.34 (1.03) mg/dL in the ND group (Table 4). Mean serum phosphate levels decreased after FC treatment initiation and were then maintained, and the levels in patients with and without comorbid HF at 104 weeks were 5.09 (1.22) mg/dL and 5.40 (1.31) mg/dL in the HD group, 5.34 (1.95) mg/dL and 5.10 (1.16) mg/dL in the PD group, and 4.70 (1.05) mg/dL and 4.90 (1.19) mg/dL in the ND group, respectively. Mean serum phosphate levels were well controlled throughout the study (Table 4 and Fig. 4).

Adverse drug reactions

Adverse drug reactions in patients with and without comorbid HF occurred in 34/166 patients (20.48%) and 289/1401 patients (20.63%) in the HD group, 16/36 patients (44.44%) and 35/173 patients (20.23%) in the PD group, and 20/146 patients (13.70%) and 131/778 patients (16.84%) in the ND group, respectively. All adverse drug reactions observed in at least two patients in either group are summarized in Table 5. The most frequently observed events in patients with and without comorbid HF were diarrhea in 2/166 patients (1.20%) and 54/1401 patients (3.85%) in the HD group, 3/36 patients (8.33%) and 10/173 patients (5.78%) in the PD group, and 6/146 patients (4.11%) and 36/778 patients (4.63%) in the ND group, followed by serum ferritin increased, which was observed in 6/166 patients (3.61%) and 43/1401 patients (3.07%) in the HD group, 4/36 patients (11.11%) and 10/173 patients (5.78%) in the PD group, and 2/146

Table 2 Changes in iron- and erythrocyte-related parameters (safety-analysis set)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
Serum ferritin [ng/mL]									
Patients with heart failure									
HD	*n*	135	93	82	56	71	63	57	50
	Absolute value, median (IQR)	44.50 (23.70, 94.60)	63.30 (35.40, 110.10)	83.45 (44.00, 122.00)	107.50 (81.55, 166.00)	115.00 (75.80, 187.00)	112.00 (71.30, 178.00)	121.80 (81.10, 187.00)	133.30 (81.80, 217.00)
	n		80	75	50	59	56	46	40
	Change from baseline, median (IQR)		7.05 (− 6.60, 26.75)	22.00 (4.00, 71.10)	52.70 (25.00, 97.00)	61.00 (30.90, 130.00)	66.10 (12.25, 107.05)	62.35 (25.00, 159.50)	71.45 (22.80, 157.80)
PD	*n*	33	24	21	15	19	15	9	7
	Absolute value, median (IQR)	146.00 (58.40, 223.60)	130.00 (67.00, 280.60)	194.00 (109.00, 266.00)	140.00 (87.00, 324.10)	219.20 (124.90, 366.00)	240.00 (174.00, 416.00)	306.00 (234.00, 351.00)	285.00 (264.20, 396.00)
	n		24	20	13	17	13	8	6
	Change from baseline, median (IQR)		14.00 (− 3.65, 63.05)	88.25 (30.75, 126.50)	84.00 (− 7.00, 116.40)	153.00 (93.40, 216.00)	187.00 (159.00, 206.30)	265.00 (190.60, 402.50)	219.50 (169.90, 273.00)
ND	*n*	108	76	69	56	53	40	22	36
	Absolute value, median (IQR)	91.00 (53.50, 122.30)	107.00 (63.65, 138.35)	124.50 (83.00, 176.90)	130.00 (92.00, 195.50)	138.00 (90.00, 200.00)	146.10 (91.25, 227.35)	165.50 (105.70, 220.00)	141.35 (75.20, 246.00)
	n		63	62	47	47	37	16	31
	Change from baseline, median (IQR)		13.00 (− 11.00, 29.40)	27.40 (6.00, 58.00)	44.00 (10.60, 97.00)	48.90 (9.80, 113.50)	57.60 (23.00, 157.20)	53.75 (45.45, 192.60)	62.00 (24.50, 187.10)
Patients without heart failure									
HD	*n*	1079	658	702	557	650	622	538	504
	Absolute value, median (IQR)	44.50 (21.10, 88.10)	57.95 (33.50, 111.00)	85.20 (46.00, 145.90)	114.00 (66.00, 183.00)	120.75 (71.40, 202.00)	124.00 (73.50, 202.20)	118.00 (69.00, 210.00)	122.65 (69.80, 231.60)
	n		542	636	519	568	551	487	442
	Change from baseline, median (IQR)		12.55 (− 3.20, 35.00)	26.90 (3.50, 67.00)	52.50 (13.80, 116.20)	63.00 (20.75, 130.25)	65.90 (18.00, 132.80)	61.00 (20.50, 139.50)	65.85 (15.20, 141.00)
PD	*n*	139	90	81	72	73	68	53	41
	Absolute value, median (IQR)	85.60 (51.00, 158.00)	100.30 (65.00, 163.10)	137.70 (67.70, 193.00)	162.95 (96.50, 284.50)	225.00 (130.70, 296.00)	216.00 (108.05, 345.00)	217.30 (146.00, 340.50)	259.00 (209.00, 415.20)
	n		83	76	62	63	61	47	37
	Change from baseline, median (IQR)		15.00 (− 4.00, 43.00)	34.25 (− 2.50, 85.90)	72.60 (27.00, 166.00)	99.00 (51.00, 192.00)	125.40 (51.60, 212.00)	132.10 (63.40, 271.00)	172.00 (112.70, 231.40)
ND	*n*	490	328	271	192	208	156	110	85
	Absolute value, median (IQR)	80.65 (41.00, 154.40)	108.50 (61.35, 181.50)	123.20 (75.00, 194.00)	155.00 (80.70, 217.20)	170.05 (95.60, 272.45)	178.40 (91.10, 262.00)	167.20 (88.70, 302.70)	196.80 (85.00, 292.00)
	n		262	229	149	171	129	85	65
	Change from baseline, median (IQR)		16.00 (− 2.00, 33.80)	30.30 (2.70, 66.90)	49.00 (21.60, 112.10)	87.00 (29.00, 157.00)	90.00 (31.00, 165.00)	98.20 (48.00, 205.6)	113.00 (50.00, 188.10)
TSAT [%]									
Patients with heart failure									
HD	*n*	128	96	78	50	67	62	52	43

Table 2 (continued)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
	Absolute value, mean (SD)	21.34 (13.30)	31.26 (16.58)	33.82 (16.68)	35.45 (14.17)	31.49 (11.28)	29.68 (12.04)	31.59 (15.21)	28.52 (13.53)
	n		84	70	46	57	53	41	33
	Change from baseline, mean (SD)		9.57 (16.38)	12.79 (15.29)	11.33 (16.67)	11.17 (14.71)	8.27 (15.39)	9.80 (16.11)	8.24 (17.36)
PD	*n*	33	25	21	14	18	15	8	6
	Absolute value, mean (SD)	28.47 (11.01)	31.62 (10.74)	37.96 (16.97)	35.88 (11.31)	41.41 (12.83)	40.99 (18.06)	41.89 (12.55)	39.40 (12.32)
	n		25	20	13	17	14	7	5
	Change from baseline, mean (SD)		4.16 (14.27)	9.55 (17.60)	4.92 (12.92)	15.01 (14.77)	16.55 (13.82)	21.64 (12.31)	19.10 (7.85)
ND	*n*	96	66	61	50	49	38	21	35
	Absolute value, mean (SD)	23.26 (13.55)	27.51 (14.87)	28.58 (13.99)	29.33 (11.73)	31.24 (12.26)	32.42 (11.02)	33.97 (12.81)	28.87 (11.75)
	n		55	53	40	41	33	14	29
	Change from baseline, mean (SD)		7.27 (14.71)	5.85 (13.90)	8.22 (13.05)	11.52 (12.32)	15.58 (11.25)	15.76 (12.49)	12.29 (12.02)
Patients without heart failure									
HD	*n*	1100	697	737	587	686	653	554	513
	Absolute value, mean (SD)	22.04 (11.95)	30.22 (13.84)	31.39 (13.10)	32.53 (13.63)	31.61 (11.89)	31.84 (12.85)	31.59 (13.00)	31.66 (13.32)
	n		640	696	553	629	605	515	469
	Change from baseline, mean (SD)		8.35 (15.01)	9.57 (14.96)	9.40 (16.01)	9.04 (14.13)	9.50 (15.18)	9.12 (14.68)	9.36 (15.80)
PD	*n*	133	94	85	73	72	62	52	41
	Absolute value, mean (SD)	30.76 (14.37)	35.72 (14.70)	35.02 (14.86)	37.51 (13.38)	39.50 (12.39)	36.78 (16.40)	41.01 (14.61)	36.92 (18.54)
	n		87	78	65	62	55	47	36
	Change from baseline, mean (SD)		5.37 (13.66)	4.96 (15.61)	7.68 (12.91)	9.67 (13.71)	7.85 (16.87)	12.28 (15.73)	8.19 (22.73)
ND	*n*	426	284	230	166	177	127	96	80
	Absolute value, mean (SD)	28.55 (12.08)	32.36 (12.74)	34.98 (13.05)	35.22 (15.17)	37.45 (15.12)	36.64 (15.50)	36.54 (15.74)	35.68 (14.25)
	n		228	192	126	142	103	73	60
	Change from baseline, mean (SD)		2.52 (12.75)	5.21 (13.16)	6.77 (13.91)	8.27 (15.50)	8.06 (14.39)	8.93 (17.26)	8.01 (15.59)
Serum iron [μg/dL]									
Patients with heart failure									
HD	*n*	133	101	82	50	69	63	52	46
	Absolute value, mean (SD)	54.27 (29.50)	76.12 (37.89)	79.22 (34.39)	81.18 (30.22)	72.54 (25.60)	68.08 (24.80)	71.46 (28.76)	64.22 (26.87)
	n		89	76	48	62	58	45	40

Table 2 (continued)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
	Change from baseline, mean (SD)		23.29 (43.42)	26.34 (35.78)	22.67 (33.48)	17.92 (33.55)	12.19 (32.16)	16.96 (35.16)	10.70 (32.55)
PD	*n*	33	26	21	15	18	15	8	6
	Absolute value, mean (SD)	72.55 (26.98)	78.50 (25.33)	92.48 (36.99)	97.53 (48.78)	105.56 (42.69)	102.13 (41.68)	99.00 (28.33)	88.33 (20.70)
	n		26	20	13	17	14	7	5
	Change from baseline, mean (SD)		7.12 (38.78)	18.90 (40.43)	14.23 (51.48)	36.82 (41.13)	36.00 (26.03)	38.86 (33.83)	33.00 (10.07)
ND	*n*	107	71	64	53	52	40	22	36
	Absolute value, mean (SD)	62.59 (33.44)	73.94 (38.07)	83.34 (35.33)	75.60 (20.16)	81.46 (26.46)	83.00 (29.24)	78.23 (33.47)	74.36 (25.95)
	n		62	58	45	45	35	16	32
	Change from baseline, mean (SD)		18.42 (41.51)	20.41 (38.13)	19.64 (31.15)	27.04 (30.52)	31.40 (38.88)	32.88 (36.70)	22.59 (34.60)
Patients without heart failure									
HD	*n*	1176	780	806	628	733	697	586	540
	Absolute value, mean (SD)	56.40 (27.36)	76.08 (37.65)	74.56 (30.88)	74.69 (30.63)	72.90 (28.32)	72.55 (30.30)	72.54 (31.69)	72.24 (36.90)
	n		710	763	593	677	653	544	499
	Change from baseline, mean (SD)		20.39 (38.22)	18.99 (34.83)	16.96 (37.05)	16.09 (34.09)	15.33 (35.84)	16.01 (37.40)	15.44 (42.28)
PD	*n*	134	98	87	77	78	64	53	41
	Absolute value, mean (SD)	76.69 (32.23)	90.53 (37.55)	86.72 (37.43)	89.36 (30.35)	89.54 (30.88)	84.17 (39.38)	92.49 (31.95)	81.29 (42.38)
	n		92	80	71	68	56	47	35
	Change from baseline, mean (SD)		13.15 (36.94)	9.71 (38.99)	14.61 (30.47)	15.21 (33.83)	11.48 (41.26)	20.55 (34.79)	8.09 (49.58)
ND	*n*	472	313	255	185	203	147	109	90
	Absolute value, mean (SD)	73.65 (31.92)	79.79 (29.95)	84.14 (29.38)	86.34 (33.74)	90.05 (35.07)	86.84 (33.98)	87.00 (34.17)	85.77 (33.02)
	n		258	221	142	163	119	77	66
	Change from baseline, mean (SD)		2.42 (36.99)	8.79 (32.04)	13.27 (36.64)	16.06 (40.93)	13.08 (34.70)	10.86 (38.46)	12.92 (39.73)
Hemoglobin [g/dL]									
Patients with heart failure									
HD	*n*	166	142	117	82	88	82	67	59
	Absolute value, mean (SD)	10.60 (1.35)	10.99 (1.33)	11.60 (1.47)	11.07 (1.25)	11.28 (1.33)	11.32 (1.34)	11.15 (1.37)	11.16 (1.26)
	n		142	117	82	88	82	67	59
	Change from baseline, mean (SD)		0.38 (1.27)	0.88 (2.00)	0.21 (1.41)	0.56 (1.75)	0.57 (1.69)	0.44 (1.59)	0.47 (1.63)
PD	*n*	36	32	28	17	22	18	12	9

Table 2 (continued)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
	Absolute value, mean (SD)	10.63 (1.39)	11.05 (1.33)	11.54 (1.19)	11.16 (0.75)	10.89 (0.96)	11.24 (1.41)	11.33 (1.06)	10.98 (1.16)
	n		32	28	17	22	18	12	9
	Change from baseline, mean (SD)		0.39 (1.31)	0.90 (1.86)	0.46 (1.10)	0.33 (1.49)	0.62 (1.66)	0.97 (1.74)	0.77 (1.58)
ND	*n*	145	118	94	77	78	61	32	43
	Absolute value, mean (SD)	10.24 (1.37)	10.78 (1.51)	11.15 (1.52)	11.19 (1.67)	11.13 (1.35)	11.35 (1.47)	11.33 (1.48)	11.13 (1.41)
	n		118	94	76	77	61	32	43
	Change from baseline, mean (SD)		0.44 (1.26)	0.83 (1.61)	0.72 (1.61)	0.64 (1.50)	0.80 (1.79)	0.99 (1.63)	0.60 (1.65)
Patients without heart failure									
HD	*n*	1384	1115	1026	861	903	838	692	635
	Absolute value, mean (SD)	10.68 (1.20)	11.21 (1.24)	11.50 (1.37)	11.19 (1.28)	11.18 (1.31)	11.20 (1.17)	11.13 (1.25)	11.21 (1.23)
	n		1115	1021	855	898	831	688	630
	Change from baseline, mean (SD)		0.52 (1.05)	0.81 (1.71)	0.48 (1.44)	0.46 (1.62)	0.47 (1.46)	0.38 (1.43)	0.47 (1.42)
PD	*n*	164	138	116	93	99	84	66	55
	Absolute value, mean (SD)	10.52 (1.24)	10.98 (1.23)	11.35 (1.50)	11.30 (1.42)	11.07 (1.26)	11.13 (1.30)	11.38 (1.27)	11.24 (1.29)
	n		137	116	93	98	84	66	55
	Change from baseline, mean (SD)		0.48 (1.17)	0.90 (1.57)	0.56 (1.57)	0.49 (1.35)	0.42 (1.50)	0.75 (1.59)	0.53 (1.58)
ND	*n*	774	579	450	341	332	258	185	149
	Absolute value, mean (SD)	10.39 (1.31)	10.72 (1.30)	11.02 (1.47)	10.96 (1.37)	11.05 (1.36)	11.15 (1.39)	11.33 (1.38)	11.49 (1.48)
	n		579	449	340	331	257	185	
	Change from baseline, mean (SD)		0.33 (1.01)	0.55 (1.43)	0.50 (1.41)	0.61 (1.45)	0.52 (1.54)	0.66 (1.54)	0.77 (1.79)

HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group; IQR, interquartile range (1st quartile, 3rd quartile); SD, standard deviation; TSAT, transferrin saturation

patients (1.37%) and 29/778 patients (3.73%) in the ND group.

Discussion

Because existing oral iron preparations have failed to improve iron-related parameters in patients with HF [12] and HF is highly prevalent in patients with CKD [1], this study evaluated the effects of FC in subgroups of CKD patients with and without comorbid HF. Regardless of the presence of comorbid HF, levels of iron- and erythrocyte-related parameters, including serum ferritin, TSAT, and hemoglobin, showed an increasing trend after the initiation of FC treatment and were then maintained during the 104-week study period. Levels of CKD-MBD-related parameters, including serum phosphate, were also well controlled. The overall time-course changes in these parameters in patients with and without comorbid HF subpopulations were similar. In particular, median changes in serum ferritin from baseline to week 36 in the PD groups were greater than those in the HD and ND

Table 3 Changes in serum ferritin and TSAT (safety-analysis set)

		Patients with heart failure				Patients without heart failure			
		Time after treatment initiation				Time after treatment initiation			
		12 weeks	36 weeks	52 weeks	104 weeks	12 weeks	36 weeks	52 weeks	104 weeks
Serum ferritin [ng/mL]									
HD	*n*	75	59	56	40	636	568	551	442
	Change from baseline, mean (SD)	33.01 (62.11)	90.98 (107.40)	67.17 (89.50)	97.16 (117.34)	39.32 (80.57)	81.86 (111.33)	89.47 (120.88)	90.70 (134.59)
	95% CI	18.72–47.30	62.99–118.97	43.20–91.14	59.63–134.68	33.05–45.59	72.68–91.03	79.36–99.59	78.11–103.28
PD	*n*	20	17	13	6	76	63	61	37
	Change from baseline, mean (SD)	80.09 (120.73)	158.64 (96.72)	194.21 (82.88)	221.82 (145.40)	35.22 (83.44)	132.91 (136.26)	128.82 (125.62)	194.46 (179.09)
	95% CI	23.59–136.59	108.91–208.36	144.12–244.29	69.23–374.41	16.15–54.29	98.59–167.23	96.65–161.00	134.75–254.17
ND	*n*	62	47	37	31	229	171	129	65
	Change from baseline, mean (SD)	43.10 (81.54)	68.06 (94.23)	97.47 (143.11)	104.88 (113.48)	40.95 (84.50)	99.75 (123.56)	102.23 (105.22)	140.21 (153.34)
	95% CI	22.39–63.80	40.40–95.73	49.75–145.18	63.25–146.50	29.95–51.95	81.10–118.40	83.90–120.56	102.21–178.20
TSAT [%]									
HD	*n*	70	57	53	33	696	629	605	469
	Change from baseline, mean (SD)	12.79 (15.29)	11.17 (14.71)	8.27 (15.39)	8.24 (17.36)	9.57 (14.96)	9.04 (14.13)	9.50 (15.18)	9.36 (15.80)
	95% CI	9.15–16.44	7.27–15.07	4.02–12.51	2.08–14.39	8.46–10.68	7.93–10.15	8.29–10.71	7.93–10.80
PD	*n*	20	17	14	5	78	62	55	36
	Change from baseline, mean (SD)	9.55 (17.60)	15.01 (14.77)	16.55 (13.82)	19.10 (7.85)	4.96 (15.61)	9.67 (13.71)	7.85 (16.87)	8.19 (22.73)
	95% CI	1.31–17.78	7.42–22.60	8.57–24.53	9.36–28.84	1.44–8.48	6.19–13.15	3.29–12.41	0.50–15.88
ND	*n*	53	41	33	29	192	142	103	60
	Change from baseline, mean (SD)	5.85 (13.90)	11.52 (12.32)	15.58 (11.25)	12.29 (12.02)	5.21 (13.16)	8.27 (15.50)	8.06 (14.39)	8.01 (15.59)
	95% CI	2.02–9.69	7.63–15.41	11.59–19.57	7.72–16.86	3.34–7.09	5.70–10.84	5.24–10.87	3.98–12.03

HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group; SD, standard deviation; CI, confidence interval

groups. Regular monitoring of serum ferritin would be necessary to prevent iron overload in patients undergoing peritoneal dialysis. There was no obvious difference in the frequency of adverse drug reactions in the HF subpopulation compared with the without HF population. In addition, the mean treatment doses of FC in patients with and without comorbid HF were comparable: 1054.5 mg/day (approximately 253.1 mg iron/day) versus 1082.6 mg/day (approximately 259.8 mg iron/day) in the HD group, 951.0 mg/day (approximately 228.2 mg iron/day) versus 976.4 mg/day (approximately 234.3 mg iron/day) in the PD group, and 896.9 mg/day (approximately 215.3 mg iron/day) versus 845.5 mg/day (approximately 202.9 mg iron)/day in the ND group, respectively.

In the IRONOUT HF study, oral polysaccharide iron was administered to patients with HF with reduced ejection fraction and iron deficiency for 16 weeks, and the median increases (95% CI) from baseline were 18 (−8, 38) ng/mL for serum ferritin and 2 (−3, 7) % for TSAT [12]. The polysaccharide iron administered in the IRONOUT HF study (150 mg twice daily; 300 mg iron/day) was comparable to the elemental iron dose administered in our study. However, the increases in the iron-related parameters from baseline to 12 weeks after FC treatment were greater in this study compared with the IRONOUT HF study. These data suggest that oral FC might be absorbed in CKD patients regardless of the presence of comorbid HF.

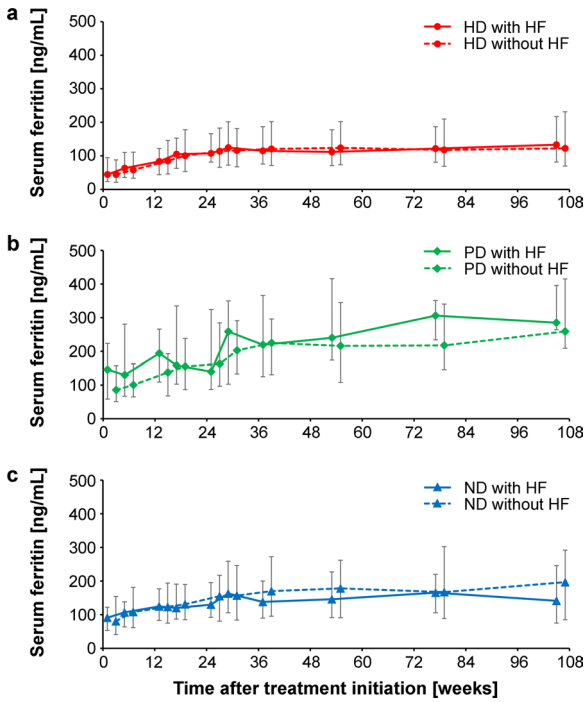

Fig. 2 Time-course changes in serum ferritin (safety-analysis set). Time-course changes in median serum ferritin. Error bars indicate the first to third quartiles. HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group

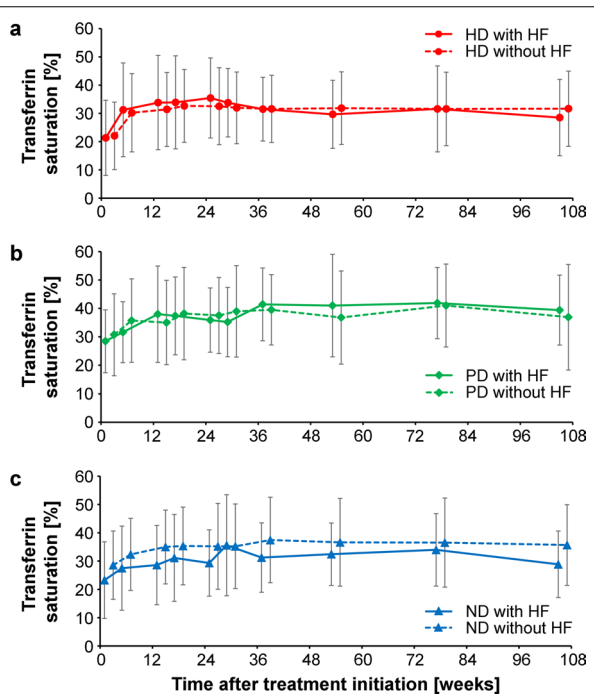

Fig. 3 Time-course changes in transferrin saturation (safety-analysis set). Time-course changes in mean transferrin saturation. Error bars indicate the standard deviation. HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group

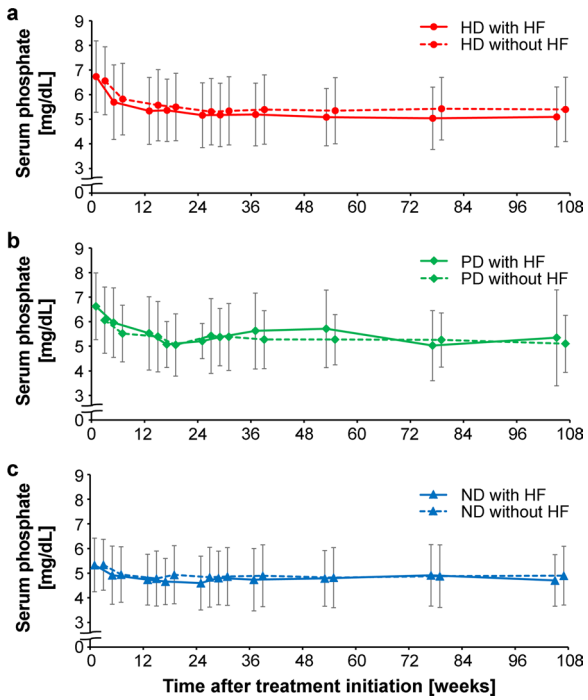

Fig. 4 Time-course changes in mean serum phosphate (effectiveness-analysis set). Time-course changes in mean serum phosphate. Error bars indicate standard deviations. HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group

A previous post hoc analysis compared the iron-related parameters of ferric citrate (Auryxia®) in non-dialysis-dependent patients with CKD and iron-deficiency anemia with or without HF [23]. They found mean (SD) increases from baseline to week 12 in serum ferritin of 201.6 (172.3) pmol/L [89.7 (76.7) ng/mL] and TSAT of 10.9 (13.7) % in patients with HF, which were comparable with changes in patients without HF. Our results in the ND group were in line with this previous report; however, the mean FC (Riona®) dose in the ND group of 896.9 mg/day (approximately 215.3 mg iron/day) was lower compared with the mean ferric citrate (Auryxia®) dose of 5000 mg/day (1050 mg iron/day) in the previous study. The difference between studies might be related to the levels of inflammation between CKD patients in the USA and Japan. Compared with the previous study, we evaluated the iron- and erythroid-related parameters based on real-world data in CKD patients with HF in Japan in the ND group as well as the HD and PD groups and obtained data related to long-term (104 weeks) FC (Riona®) treatment.

Anemia or iron deficiency is associated with an increased risk of mortality in patients with CKD and patients with HF [3, 5–8, 26]. The CKDopps study [26]

Table 4 Changes in chronic kidney disease—mineral and bone disorder-related parameters (effectiveness-analysis set)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
Serum phosphate [mg/dL]									
Patients with heart failure									
HD	*n*	146	127	112	77	83	77	64	59
	Absolute value, mean (SD)	6.73 (1.45)	5.69 (1.52)	5.34 (1.36)	5.16 (1.32)	5.19 (1.27)	5.09 (1.17)	5.04 (1.27)	5.09 (1.22)
	n		127	112	77	83	77	64	59
	Change from baseline, mean (SD)		− 1.10 (1.38)	− 1.36 (1.47)	− 1.55 (1.51)	− 1.40 (1.55)	− 1.46 (1.56)	− 1.55 (1.90)	− 1.55 (1.62)
PD	*n*	33	31	27	17	22	18	12	9
	Absolute value, mean (SD)	6.62 (1.36)	5.96 (1.42)	5.53 (1.49)	5.21 (0.72)	5.62 (1.54)	5.71 (1.58)	5.03 (1.42)	5.34 (1.95)
			31	27	17	22	18	12	9
	Change from baseline, mean (SD)		− 0.61 (1.13)	− 1.09 (1.42)	− 1.24 (1.31)	− 1.03 (1.43)	− 0.84 (1.15)	− 1.47 (1.40)	− 1.31 (1.13)
ND	*n*	124	103	85	71	74	59	32	44
	Absolute value, mean (SD)	5.33 (1.09)	4.92 (1.18)	4.74 (1.03)	4.60 (1.09)	4.74 (1.26)	4.79 (1.13)	4.91 (1.25)	4.70 (1.05)
	n		103	85	71	74	59	32	44
	Change from baseline, mean (SD)		− 0.44 (1.00)	− 0.49 (0.91)	− 0.49 (1.26)	− 0.34 (1.24)	− 0.22 (1.16)	− 0.07 (1.34)	− 0.23 (1.09)
Patients without heart failure									
HD	*n*	1223	1012	945	810	850	798	674	631
	Absolute value, mean (SD)	6.56 (1.38)	5.82 (1.45)	5.57 (1.45)	5.31 (1.35)	5.39 (1.41)	5.35 (1.34)	5.43 (1.27)	5.40 (1.31)
	n		1011	940	806	847	793	671	627
	Change from baseline, mean (SD)		− 0.76 (1.48)	− 0.96 (1.54)	− 1.17 (1.61)	− 1.14 (1.70)	− 1.18 (1.63)	− 1.13 (1.62)	− 1.17 (1.62)
PD	*n*	144	125	106	88	89	77	63	53
	Absolute value, mean (SD)	6.06 (1.35)	5.51 (1.16)	5.39 (1.43)	5.42 (1.52)	5.27 (1.17)	5.27 (1.02)	5.26 (1.10)	5.10 (1.16)
	n		125	106	88	89	77	63	53
	Change from baseline, mean (SD)		− 0.58 (1.32)	− 0.72 (1.40)	− 0.74 (1.53)	− 0.69 (1.46)	− 0.77 (1.48)	− 0.80 (1.49)	− 1.06 (1.72)
ND	*n*	657	499	399	308	312	249	181	149
	Absolute value, mean (SD)	5.34 (1.03)	4.95 (1.13)	4.78 (1.12)	4.84 (1.21)	4.90 (1.26)	4.82 (1.22)	4.88 (1.27)	4.90 (1.19)
	n		499	398	307	312	248	181	149
	Change from baseline, mean (SD)		− 0.44 (0.99)	− 0.51 (1.10)	− 0.37(1.16)	− 0.23 (1.27)	− 0.27 (1.19)	− 0.16 (1.22)	− 0.16 (1.22)
Corrected Ca [mg/dL]									
Patients with heart failure									
HD	*n*	146	127	112	77	83	77	64	59

Table 4 (continued)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
	Absolute value, mean (SD)	8.55 (0.77)	8.66 (0.68)	8.68 (0.75)	8.65 (0.73)	8.57 (0.79)	8.69 (0.64)	8.64 (0.66)	8.66 (0.72)
	n		127	112	77	83	77	64	59
	Change from baseline, mean (SD)		0.12 (0.63)	0.14 (0.78)	0.10 (0.81)	0.02 (0.91)	0.23 (0.80)	0.14 (0.81)	0.15 (0.75)
PD	*n*	33	31	27	17	22	18	12	9
	Absolute value, mean (SD)	8.25 (0.80)	8.37 (0.66)	8.61 (0.66)	8.49 (0.67)	8.54 (0.70)	8.23 (0.73)	8.51 (0.86)	8.46 (0.68)
	n		31	27	17	22	18	12	9
	Change from baseline, mean (SD)		0.05 (0.65)	0.25 (0.70)	0.09 (0.87)	0.20 (0.96)	−0.25 (0.88)	0.27 (1.22)	0.17 (1.21)
ND	*n*	122	103	84	70	73	59	32	44
	Absolute value, mean (SD)	8.38 (0.69)	8.49 (0.69)	8.57 (0.67)	8.49 (0.74)	8.48 (0.72)	8.61 (0.81)	8.72 (0.61)	8.63 (0.72)
	n		102	84	69	72	59	32	44
	Change from baseline, mean (SD)		0.12 (0.46)	0.16 (0.53)	0.04 (0.62)	−0.02(0.60)	0.13 (0.70)	0.25 (0.67)	0.02 (0.70)
Patients without heart failure									
HD	*n*	1222	1010	943	809	850	798	672	631
	Absolute value, mean (SD)	8.73 (0.81)	8.76 (0.75)	8.78 (0.72)	8.80 (0.70)	8.76 (0.75)	8.77 (0.73)	8.75 (0.67)	8.74 (0.70)
	n		1009	938	806	847	793	669	627
	Change from baseline, mean (SD)		0.04 (0.68)	0.09 (0.74)	0.11 (0.85)	0.05 (0.90)	0.07 (0.86)	0.05 (0.90)	0.01 (0.90)
PD	*n*	142	123	106	88	89	77	63	55
	Absolute value, mean (SD)	8.5 (0.78)	8.57 (0.67)	8.54 (0.69)	8.59 (0.78)	8.6 (0.72)	8.64 (0.77)	8.54 (0.63)	8.55 (0.73)
	n		123	106	88	88	77	63	55
	Change from baseline, mean (SD)		0.10 (0.55)	0.04 (0.67)	0.09 (0.81)	0.09 (0.85)	0.14 (0.91)	−0.03 (0.85)	0.00 (1.02)
ND	*n*	656	500	399	309	312	249	181	148
	Absolute value, mean (SD)	8.56 (0.80)	8.60 (0.77)	8.62 (0.96)	8.62 (0.72)	8.66 (0.79)	8.75 (0.68)	8.73 (0.77)	8.78 (0.71)
	n		499	398	307	312	248	181	148
	Change from baseline, mean (SD)		0.05 (0.60)	0.04 (0.79)	−0.01 (0.68)	−0.01 (0.75)	0.02 (0.70)	−0.05 (0.91)	0.02 (0.92)
Intact PTH [pg/mL]									
Patients with heart failure									
HD	*n*	104	66	70	44	57	54	51	44
	Absolute value, median (IQR)	158.00 (99.00, 269.50)	149.50 (98.00, 238.00)	134.00 (77.00, 216.00)	179.50 (90.50, 258.00)	142.00 (70.00, 237.00)	136.50 (86.00, 214.00)	119.00 (79.00, 206.00)	108.50 (66.50, 177.00)
	n		54	63	40	51	48	42	37

Table 4 (continued)

		Time after treatment initiation							
		Baseline	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**	**76 weeks**	**104 weeks**
	Change from baseline, median (IQR)		−17.00 (−69.00, 1.00)	−22.00 (−82.00, 14.00)	−1.00 (−56.50, 77.50)	−12.00 (−127.00, 40.00)	−17.00 (−116.00, 27.50)	−15.00 (−94.00, 43.00)	−26.00 (−104.00, 17.00)
PD	*n*	26	22	19	15	17	15	11	8
	Absolute value, median (IQR)	171.00 (110.00, 339.00)	199.50 (89.00, 313.00)	163.00 (59.00, 228.00)	107.00 (52.00, 284.00)	194.00 (87.00, 259.00)	194.00 (89.00, 231.00)	137.00 (114.00, 230.00)	164.50 (122.00, 194.50)
	n		20	18	13	16	14	9	6
	Change from baseline, median (IQR)		−12.00 (−61.00, 30.00)	−34.00 (−136.00, 5.00)	0.00 (−25.00, 11.00)	−12.00 (−171.00, 53.50)	−9.00 (−89.00, 37.00)	−13.00 (−315.00, 4.00)	29.50 (−79.00, 73.00)
ND	*n*	63	41	46	44	46	38	17	32
	Absolute value, median (SD)	194.00 (106.00, 296.00)	194.00 (112.00, 265.00)	148.00 (106.00, 219.00)	157.00 (105.50, 256.50)	187.50 (122.00, 290.00)	148.00 (85.00, 229.00)	162.00 (96.00, 198.00)	167.00 (99.50, 222.00)
	n		30	40	31	32	26	7	22
	Change from baseline, median (IQR)		−11.50 (−85.00, 30.00)	−14.50 (−47.50, 7.00)	−26.00 (−76.00, 14.00)	−24.00 (−57.00, 29.00)	−5.50 (−59.00, 32.00)	−66.00 (−89.00, −10.00)	20.50 (−5.00, 39.00)
Patients without heart failure									
HD	*n*	878	555	579	480	544	552	512	487
	Absolute value, median (IQR)	177.00 (106.00, 267.00)	163.00 (95.00, 245.00)	150.00 (92.00, 237.00)	144.00 (85.50, 214.00)	145.00 (92.50, 218.50)	145.50 (97.00, 222.50)	158.00 (92.00, 233.00)	154.00 (90.00, 220.00)
	n		465	525	439	473	482	442	416
	Change from baseline, median (IQR)		−10.00 (−58.00, 25.00)	−13.00 (−66.00, 29.00)	−15.00 (−81.00, 38.00)	−12.00 (−95.00, 40.00)	−13.00 (−88.00, 38.00)	−9.50 (−97.00, 45.00)	−11.50 (−105.00, 50.50)
PD	*n*	94	67	61	61	51	48	42	38
	Absolute value, median (IQR)	193.50 (102.00, 371.00)	186.00 (86.00, 294.00)	177.00 (91.00, 318.00)	199.00 (102.00, 341.00)	167.00 (83.00, 249.00)	164.00 (80.00, 277.5)	195.00 (91.00, 329.00)	143.00 (83.00, 213.00)
	n		62	54	53	41	41	34	31
	Change from baseline, median (IQR)		−7.00 (−60.00, 29.00)	9.00 (−69.00, 52.00)	13.00 (−90.00, 86.00)	2.00 (−129.00, 90.00)	−1.00 (−118.00, 94.00)	5.00 (−169.00, 145.00)	−18.0 (−234.00, 106.00)
ND	*n*	261	167	148	127	135	106	86	71
	Absolute value, median (SD)	228.00 (117.00, 373.00)	215.00 (121.00, 350.00)	210.00 (116.00, 337.50)	233.00 (122.00, 363.00)	211.00 (101.00, 367.00)	201.00 (100.00, 330.00)	193.50 (114.00, 295.00)	154.00 (98.00, 290.00)
	n		119	109	84	79	63	45	40
	Change from baseline, median (IQR)		−8.00 (−38.00, 31.00)	4.00 (−44.00, 38.00)	18.00 (−42.00, 58.00)	1.00 (−43.00, 47.00)	14.00 (−42.00, 76.00)	6.00 (−56.00, 63.00)	−7.00 (−92.00, 56.00)

HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group; SD, standard deviation; PTH, parathyroid hormone; IQR, interquartile range (1st quartile, 3rd quartile)

and subgroup analyses of the CRIC study [27] reported that a lower TSAT was associated with higher risks of mortality and cardiovascular events in non-dialysis-dependent CKD patients. In the current study, FC had a tendency to increase the level of TSAT in CKD patients with and without HF, which may reduce the risks of mortality and cardiovascular events. In a mouse model of CKD, the administration of ferric citrate (Auryxia®) increased the TSAT and serum ferritin levels and improved cardiac markers, including B-type natriuretic peptide, atrial natriuretic peptide, and b-myosin heavy chain, and prolonged survival [28].

Table 5 Adverse drug reactions observed in at least two patients in either group (safety-analysis set)

	Patients with heart failure			Patients without heart failure		
	HD	PD	ND	HD	PD	ND
Safety-analysis set, *n*	166	36	146	1401	173	778
Patients with any adverse drug reaction, *n* (%)	34 (20.48)	16 (44.44)	20 (13.70)	289 (20.63)	35 (20.23)	131 (16.84)
Number of adverse drug reactions	49	23	25	396	44	163
Adverse drug reactions, n (%)						
Diarrhea	2 (1.20)	3 (8.33)	6 (4.11)	54 (3.85)	10 (5.78)	36 (4.63)
Serum ferritin increased	6 (3.61)	4 (11.11)	2 (1.37)	43 (3.07)	10 (5.78)	29 (3.73)
Constipation	0 (0.00)	2 (5.56)	3 (2.05)	28 (2.00)	1 (0.58)	11 (1.41)
Hemoglobin increased	2 (1.20)	0 (0.00)	1 (0.68)	31 (2.21)	0 (0.00)	0 (0.00)
Nausea	1 (0.60)	0 (0.00)	0 (0.00)	18 (1.28)	1 (0.58)	10 (1.29)
Hyperferritinemia	1 (0.60)	2 (5.56)	1 (0.68)	10 (0.71)	3 (1.73)	8 (1.03)
Hypertension	1 (0.60)	1 (2.78)	0 (0.00)	11 (0.79)	1 (0.58)	3 (0.39)
Abdominal discomfort	1 (0.60)	0 (0.00)	0 (0.00)	11 (0.79)	0 (0.00)	3 (0.39)
Abdominal distension	2 (1.20)	0 (0.00)	0 (0.00)	7 (0.50)	0 (0.00)	3 (0.39)
Feces discolored	1 (0.60)	0 (0.00)	0 (0.00)	11 (0.79)	0 (0.00)	0 (0.00)
Polycythemia	2 (1.20)	0 (0.00)	0 (0.00)	10 (0.71)	0 (0.00)	0 (0.00)
Decreased appetite	0 (0.00)	0 (0.00)	1 (0.68)	5 (0.36)	1 (0.58)	3 (0.39)
Pruritus	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.36)	0 (0.00)	3 (0.39)
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	7 (0.50)	1 (0.58)	0 (0.00)
Feces soft	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.43)	0 (0.00)	2 (0.26)
Abdominal pain	1 (0.60)	0 (0.00)	1 (0.68)	3 (0.21)	1 (0.58)	1 (0.13)
Hepatic function abnormal	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	2 (1.16)	3 (0.39)
Blood iron increased	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	1 (0.58)	2 (0.26)
Gastroesophageal reflux disease	0 (0.00)	0 (0.00)	1 (0.68)	3 (0.21)	1 (0.58)	0 (0.00)
Red blood cell count increased	1 (0.60)	0 (0.00)	0 (0.00)	4 (0.29)	0 (0.00)	0 (0.00)
Renal impairment	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.64)
Hyperphosphatemia	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	2 (0.26)
Hypocalcemia	0 (0.00)	0 (0.00)	2 (1.37)	1 (0.07)	1 (0.58)	0 (0.00)
Abdominal pain upper	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	1 (0.58)	1 (0.13)
Acute myocardial infarction	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.21)	0 (0.00)	0 (0.00)
Anemia	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	1 (0.13)
Arrhythmia	0 (0.00)	0 (0.00)	2 (1.37)	1 (0.07)	0 (0.00)	0 (0.00)
Back pain	1 (0.60)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Blood calcium decreased	1 (0.60)	1 (2.78)	0 (0.00)	1 (0.07)	0 (0.00)	0 (0.00)
Cardiac failure congestive	0 (0.00)	0 (0.00)	1 (0.68)	2 (0.14)	0 (0.00)	0 (0.00)
Cerebral infarction	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.21)	0 (0.00)	0 (0.00)
Death	0 (0.00)	1 (2.78)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Feeling abnormal	1 (0.60)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Hematocrit increased	1 (0.60)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Hemoglobin decreased	2 (1.20)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	0 (0.00)
Headache	1 (0.60)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Hyperuricemia	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	1 (0.13)
Hypophosphatemia	1 (0.60)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Malaise	0 (0.00)	1 (2.78)	0 (0.00)	1 (0.07)	1 (0.58)	0 (0.00)
Shunt occlusion	1 (0.60)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Blood phosphorus increased	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	1 (0.58)	0 (0.00)
Transferrin saturation increased	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.21)	0 (0.00)	0 (0.00)
Nephrogenic anemia	1 (0.60)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Abdominal pain lower	1 (0.60)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	0 (0.00)

Table 5 (continued)

	Patients with heart failure			Patients without heart failure		
	HD	PD	ND	HD	PD	ND
Angina pectoris	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Blood parathyroid hormone increased	0 (0.00)	1 (2.78)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.13)
Blood pressure decreased	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Blood pressure increased	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Bronchitis	1 (0.60)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	0 (0.00)
Cerebellar infarction	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Eosinophilia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.26)
Frequent bowel movements	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Gastric ulcer	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Gastrointestinal disorder	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Hypercholesterolemia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.13)
Insomnia	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Muscle spasms	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	1 (0.58)	0 (0.00)
Musculoskeletal pain	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Nasopharyngitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Oedema	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.26)
Pain in extremity	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Peritonitis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	1 (0.58)	0 (0.00)
Stomatitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Shunt stenosis	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
Peripheral arterial occlusive disease	2 (1.20)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

HD, hemodialysis group; PD, peritoneal dialysis group; ND, non-dialysis-dependent group

This study had important limitations. The case report forms used in this study lacked several important pieces of information, including detailed information on HF (e.g., HFrEF, HFpEF, and the severity of HF, such as the New York Heart Association functional classification, and were not adjusted by an independent committee), levels of hepcidin and CRP, and use of intravenous iron preparations or ESA dosage. In addition, because of an observational real-world study, missing data were observed and approximately 13% of patients with and without HF ($n=45/348$ (12.9%) and $n=309/2352$ (13.1%), respectively) were lost to follow-up and therefore we did not determine the reasons for dropping out of the study. Thus, the excluded patients might have been more likely to be resistant to iron replacement by the oral iron therapy. Further prospective, randomized, controlled studies are needed to confirm the iron absorption effect of oral FC in patients with HF.

Conclusions

This long-term, real-world, post-marketing surveillance study demonstrated that oral FC administration had a tendency to increase iron-related parameters in CKD patients regardless of the presence of HF.

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Author contributions
All authors contributed to the study conception and design. Data collection and analysis were performed by Kenjiro Murakami, Ryoichi Yamada, and Hiroyuki Susai. The first draft of the manuscript was prepared by Kyoko Ito, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This observational post-marketing surveillance study was conducted in accordance with the Good Post-Marketing Study Practice (GPSP) of the Ministry of Health, Labour, and Welfare in Japan. The data were anonymized and collected within general clinical practice, and the requirement for informed consent was therefore waived.

Consent for publication
Not applicable.

Competing interests
Kyoko Ito and Noriaki Nishino are employees of Torii Pharmaceutical Co., Ltd., and Kenjiro Murakami, Ryoichi Yamada, and Hiroyuki Susai are employees of Japan Tobacco Inc.

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