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Long-Term Safety and Efficacy of JR-131, a Biosimilar of Darbepoetin Alfa, in Japanese Patients With Renal Anemia Undergoing Hemodialysis: Phase 3 Prospective Study

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Abstract: The objective of this study was to evaluate the safety and efficacy of JR-131, a biosimilar of darbepoetin alfa, for long-term treatment of renal anemia patients undergoing hemodialysis. In this multicenter, single-arm, phase 3 study, 159 patients with renal anemia who had been receiving darbepoetin alfa or recombinant human erythropoietins were treated with intravenous JR-131 for 52 weeks. In patients receiving darbepoetin alfa, JR-131 was administered at the same dose, while in patients receiving recombinant human erythropoietin the dose was determined based on the 1:200 conversion ratio following the Japanese darbepoetin alfa package insert. No notable adverse drug reactions were reported, and no anti-JR-131 antibodies were detected. The hemoglobin levels were maintained in the range of 10.0–12.0 g/dL throughout the study. JR-131 proved to be a useful and lower-cost alternative to darbepoetin alfa in the management of renal anemia in patients undergoing hemodialysis. **Key Words:** Biosimilar, Darbepoetin alfa, Erythropoiesis-stimulating agent, JR-131, Long-term study.

Renal anemia in patients with chronic kidney disease (CKD), particularly in patients undergoing hemodialysis, is associated with increased risks of poor quality of life, hospitalization, cardiac morbidity, and all-cause mortality (1–3). Erythropoiesis-stimulating agents (ESAs) (4–6) are the standard treatment for renal anemia in patients with CKD and are used in almost 90% of Japanese patients undergoing hemodialysis (7). Five ESAs are currently available: epoetin alfa, epoetin beta, epoetin kappa, darbepoetin alfa, and epoetin beta pegol. Dialysis patients receiving ESAs often require lifelong treatment for their renal anemia. Unfortunately, the number of dialysis patients in Japan continues to rise every year; at the end of 2016, the number of dialysis patients has reached 329 609 (8). Although the cost of ESAs is included in the payment of dialysis, the introduction of lower-cost ESA biosimilars has been desired to decrease dialysis costs (9). In 2010, epoetin kappa, a biosimilar of epoetin alfa, developed by JCR Pharmaceuticals (Ashiya, Japan) and Kissei Pharmaceutical (Matsumoto, Japan) was approved as the only ESA biosimilar in Japan (10). However, among ESAs, until now darbepoetin alfa has been the most common ESA in Japan due to its less frequent administration than the epoetins (11).

JR-131 is the first domestic-produced biosimilar of darbepoetin alfa developed by JCR Pharmaceuticals and Kissei Pharmaceutical. JR-131 is produced by recombinant DNA technology in completely serum-free medium without using any animal-derived material. JR-131 has been developed in accordance with the Guideline for Quality, Safety, and Efficacy Assurance of Follow-on Biologics issued in 2009 by the Japanese regulatory authorities (12). The quality of JR-131 was confirmed identical to those of the reference product, darbepoetin alfa. The preclinical

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comparative studies on pharmacology, pharmacokinetics, and toxicology revealed similarities of JR-131 to darbepoetin alfa. Previously, in a phase 1 clinical trial in healthy Japanese male volunteers, the pharmacokinetics, tolerability, and safety of JR-131 were equivalent/similar to those of darbepoetin alfa, when administered intravenously or subcutaneously. Then, the phase 3 clinical trial of JR-131 in patients with renal anemia undergoing hemodialysis conducted in Japan revealed that JR-131 was clinically equivalent to darbepoetin alfa (21).

The study objective was to evaluate the safety and efficacy of JR-131 in the long-term treatment of renal anemia in patients with CKD undergoing hemodialysis during a phase 3 study.

PATIENTS AND METHODS

Study design

This was a long-term (52-weeks), multicenter, prospective, single-arm study in patients with renal anemia undergoing hemodialysis conducted at 14 sites from September 2016 to March 2018 in Japan. The study protocol, informed consent form, and other relevant study documentations were approved by the institutional review board at each participating study site. All patients provided written informed consent before initiation of any study-specific procedure. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines. The study was designed and conducted by the sponsors (JCR Pharmaceuticals and Kissei Pharmaceutical) in collaboration with the principal investigators. The study is registered with ClinicalTrials.gov.: NCT02912533.

Patients

The study consisted of a 4-week observation period and a 52-week treatment period with JR-131. Male or female patients aged ≥20 years with ESRD who were diagnosed with renal anemia were included. The inclusion criteria before starting the observation period were patients undergoing maintenance hemodialysis three times a week for ≥12 weeks; receiving intravenous darbepoetin alfa weekly or biweekly for ≥4 weeks, or recombinant human erythropoietin (rHuEPO) including epoetin alfa, beta or kappa at a dose of ≤9000 IU/week two to three times a week for ≥4 weeks; and hemoglobin (Hb) level within the range of 9.5–12.5 g/dL measured before the first dialysis of the week for 4 weeks. Other inclusion criteria were patients receiving a constant dose of darbepoetin alfa or rHuEPO, having a mean Hb level of ≥10.0 g/dL to <12.0 g/dL measured before the first dialysis of the week during the observation period; transferrin saturation (TSAT) level ≥ 20% or ferritin level ≥ 100 ng/mL at the start of the observation period; and dialysis conditions including frequency, the method of dialysis, and dialysis time were maintained throughout the study. The main exclusion criteria were hardly controllable hypertension; a serious illness or medical condition; obvious hemorrhagic lesions such as systemic blood disease, hemolytic anemia, or gastrointestinal hemorrhage; hypersensitivity to ESAs; receiving erythrocyte transfusion during 16 weeks before the observation period; or receiving ESAs other than darbepoetin alfa or rHuEPOs, receiving a protein anabolic hormone, testosterone enanthate, mepitiostane, levocarnitine, a zinc-containing preparation, or a copper-containing preparation for 16 weeks before the observation period. Patients who met the eligibility criteria entered a 4-week observation period. Subjects received darbepoetin alfa or rHuEPO through the venous side of the dialysis circuit at end of the hemodialysis. Darbepoetin alfa or rHuEPO was administered during the observation period. Once eligibility was confirmed at the end of the observation period, subjects entered the 52-week treatment period.

Dose and treatment

Darbepoetin alfa or rHuEPO were administered at a constant dose and regimen during the observation period. Subsequently, JR-131 was administered through the venous side of the dialysis circuit at the end of the first dialysis of the week for 52 weeks. In patients receiving darbepoetin alfa during the observation period, JR-131 treatment started at darbepoetin alfa same dose and regimen as darbepoetin alfa. The starting dose of JR-131 for patients that switched from rHuEPO was determined according to the 1:200 conversion ratio (1 μg of JR-131 = 100–225 IU of epoetin) in accordance with the Japanese package insert of darbepoetin alfa (13) as shown in Table 1. After treatment with the first dose of JR-131, the dose was adjusted to maintain the hemoglobin (Hb) level within the target range (≥10.0 g/dL to <12.0 g/dL) according to the dose adjustment table (Table 1). Dose adjustment was not allowed within the first 2 weeks after switching to JR-131. Dose increase or reduction should be performed one-step at a time, and dose adjustments were prohibited for 2 weeks. Dose adjustment within one or more steps or drug interruption due to treatment-emergent adverse events (TEAEs) was allowed if the investigator believed it was

TABLE 1. *Dose conversion from rHuEPO to JR-131 and dose adjustment for JR-131*

	rHuEPO/week at secondary enrollment	JR-131 (μg)
Dose conversion for switching from rHuEPO to JR-131	<3000 IU	15
	3001–4500 IU	20
	4501–6000 IU	30
	6001–9000 IU	40
Dose adjustment for JR-131	Step 1	5
	Step 2	10
	Step 3	15
	Step 4	20
	Step 5	30
	Step 6	40
	Step 7	50
	Step 8	60
	Step 9	80
	Step 10	100
	Step 11	120
	Step 12	140
	Step 13	160
	Step 14	180

IU, International unit; rHuEPO, recombinant human erythropoietin.

necessary. When Hb level ≥ 12.0 g/dL at the minimal dose (5 μg) in two consecutive measurements, JR-131 administration was interrupted. The same dose administration was used when the treatment was restarted after drug interruption. When Hb level was <9.5 g/dL at the maximal dose (180 μg) in two consecutive measurements, the same dose of 180 μg was administered the next week. Patients were withdrawn from the study, when Hb level was <9.0 g/dL or > 12.5 g/dL in two consecutive measurements, when Hb level was <9.5 g/dL at the maximum dose (180 μg) in four consecutive measurements, or when the administration of JR-131 was suspended over four consecutive weeks. Iron preparation was allowed to be administered as a guide of TSAT <20% or ferritin <100 ng/mL. Medication with ESAs other than darbepoetin alfa or rHuEPO, an anabolic protein hormone, testosterone enanthate, mepitiostane, levocarnitine, a zinc-containing preparation, a copper-containing preparation, any investigational product other than JR-131, and erythrocyte transfusion were prohibited throughout the study.

Safety and efficacy assessments

Safety was assessed according to the incidence and severity of TEAEs, laboratory tests (hematology, biochemistry, and iron-related parameters including serum iron, total iron binding capacity, ferritin, and TSAT), vital signs, body weight, and 12-lead electrocardiogram (ECG). TEAE was defined as an event that appeared after the start of the treatment with JR-131, which was absent before the observation period or worsened during the observation period. The anti-JR-131 antibody was tested using electrochemiluminescence at week 0, week 28, and week 52. If positive, the neutralizing antibody was tested. The efficacy parameters evaluated were Hb levels, the proportion of the target Hb maintenance, administered dose, and observed dose conversion ratio switching from rHuEPO to JR-131. The target Hb level was within the range of ≥10.0 g/dL to <12.0 g/dL, which is the recommended Hb target by

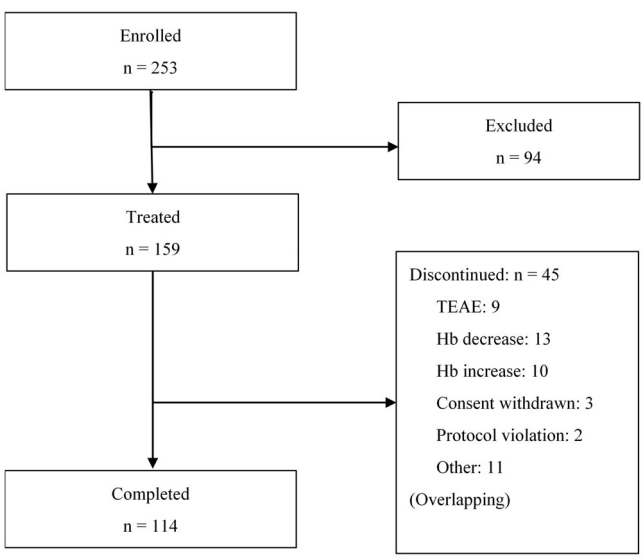

FIG. 1. Patient disposition.Hb, hemoglobin.

TABLE 2. *Patients demographics and clinical characteristics at baseline (FAS:* N = *157)*

	n (%)
Sex, *n* (%)	
Male	115 (73.2)
Female	42 (26.8)
Age (years)	
Mean ± SD (min, med, max)	64.3 ± 12.8 (28, 65, 87)
<65, *n* (%)	71 (45.2)
≥65, *n* (%)	86 (54.8)
Dry weight (kg)	
Mean ± SD (min, med, max)	60.64 ± 13.08 (35.0, 59.0, 109.0)
Method of dialysis	
Hemodialysis	97 (61.8)
Hemodiafiltration	60 (38.2)
Duration of dialysis (months)	
Mean ± SD (min, med, max)	85.8 ± 73.7 (4, 62, 357)
Primary cause CKD (overlapping), *n*	
Diabetic nephropathy	60
Chronic glomerulonephritis	43
Nephrosclerosis	27
Polycystic kidney	11
Chronic pyelonephritis	0
Others	7
Unknown	13
ESA before switching to JR-131	
rHuEPO	96 (61.1)
Epoetin alfa, *n* (%)	0 (0.0)
Epoetin beta, *n* (%)	28 (17.8)
Epoetin kappa, *n* (%)	68 (43.3)
Darbepoetin alfa	61 (38.9)
Weekly administration, *n* (%)	56 (35.7)
Biweekly administration, *n* (%)	5 (3.2)
ESA dose before switching to JR-131 rHuEPO (IU/week)	
Mean ± SD (min, med, max)	4382.8 ± 2225.7 (1500, 4500, 9000)
≤1500, *n* (%)	14 (8.9)
1500< to ≤3000, *n* (%)	24 (15.3)
3000< to ≤4500, *n* (%)	28 (17.8)
4500< to ≤9000, *n* (%)	30 (19.1)
Weekly darbepoetin alfa (μg)	
Mean ± SD (min, med, max)	21.1 ± 25.6 (5, 15, 180)
5, *n* (%)	9 (5.7)
10, *n* (%)	18 (11.5)
15, *n* (%)	7 (4.5)
20, *n* (%)	7 (4.5)
30, *n* (%)	9 (5.7)
40, *n* (%)	2 (1.3)
60, *n* (%)	3 (1.9)
180, *n* (%)	1 (0.6)
Biweekly darbepoetin alfa (μg)	
Mean ± SD (min, med, max)	40.0 ± 36.7 (10, 20, 80)
10, *n* (%)	2 (1.3)
20, *n* (%)	1 (0.6)
80, *n* (%)	2 (1.3)
Baseline hemoglobin level (g/dL)	
Mean ± SD (min, med, max)	10.88 ± 0.51 (9.5, 10.8, 12.2)
Baseline hematocrit (%)	
Mean ± SD (min, med, max)	31.76 ± 2.00 (26.1, 31.8, 38.1)
Baseline ferritin (μg/L)	
Mean ± SD (min, med, max)	154.89 ± 127.77 (8.9, 113.0, 716.0)
Baseline transferrin saturation (%)	
Mean ± SD (min, med, max)	27.89 ± 9.80 (10.8, 26.2, 70.9)

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; FAS, full analysis set; IU, international unit; Max, maximum; Med, median; Min, minimum; rHuEPO, recombinant human erythropoietin; SD, standard deviation.

the 2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease (6).

Statistical analysis

A sample size of 100 patients was planned in accordance with the International Council for Harmonization Guideline E1, the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-life-threatening Conditions.

Safety analysis was performed for subjects in the safety set (SS), and efficacy was analyzed for the full analysis set (FAS). The SS consisted of subjects excluding those with GCP non-compliance, no administration of the study drug, and discontinuation before treatment initiation. The FAS included the SS subjects (except those that had no evaluable Hb level). TEAEs were coded using the Medical Dictionary for Regulatory Activities (version. 19.1). Continuous variables were summarized as mean, SD, two-sided 95% confidence interval (CI), minimum, median, and maximum, and categorical data as a percentage.

Hb level and administered dose at the time of assessment were analyzed for the following subgroups: sex, age (<65 years/≥65 years), and treatment for renal anemia during the observation period with ESAs (darbepoetin alfa, rHuEPO including erythropoietin alfa, beta, and kappa). Baseline variables were defined as the mean variables at week −3, −2, −1, and 0 of the observation period. All analyses were performed using SAS software ver. 9.4 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

The study was conducted at 14 sites in Japan. Among the 253 patients enrolled in the study, 159 patients received JR-131, and 114 patients completed the 52-week treatment. Forty-five patients discontinued due to TEAEs (*n* = 9), decrease of Hb

TABLE 3. *Number and percentage of patients with treatment-emergent adverse events and adverse drug reactions classified by primary system organ class and preferred term (preferred term incidence ≥ 5%) (SS:* N = *159)*[†]

Primary system organ class	Treatment-emergent adverse events			Adverse drug reactions		
Preferred term	*n*	(%)	Events	*n*	(%)	Events
Total	147	(92.5)	1086	4	(2.5)	4
Infections and infestations	115	(72.3)	315	0	(0.0)	0
Gastroenteritis	10	(6.3)	12	0	(0.0)	0
Nasopharyngitis	97	(61.0)	213	0	(0.0)	0
Nervous system disorders	40	(25.2)	57	0	(0.0)	0
Loss of consciousness	8	(5.0)	9	0	(0.0)	0
Vascular disorders	25	(15.7)	32	1	(0.6)	1
Orthostatic hypotension	8	(5.0)	11	0	(0.0)	0
Gastrointestinal disorders	76	(47.8)	126	0	(0.0)	0
Diarrhea	25	(15.7)	34	0	(0.0)	0
Vomiting	14	(8.8)	24	0	(0.0)	0
Skin and subcutaneous tissue disorders	51	(32.1)	75	0	(0.0)	0
Hemorrhage subcutaneous	8	(5.0)	14	0	(0.0)	0
Pruritus	10	(6.3)	10	0	(0.0)	0
Musculoskeletal and connective tissue disorders	65	(40.9)	104	0	(0.0)	0
Arthralgia	12	(7.5)	15	0	(0.0)	0
Back pain	13	(8.2)	15	0	(0.0)	0
Musculoskeletal pain	13	(8.2)	14	0	(0.0)	0
Pain in extremity	14	(8.8)	15	0	(0.0)	0
Injury, poisoning, and procedural complications	81	(50.9)	166	0	(0.0)	0
Excoriation	14	(8.8)	18	0	(0.0)	0
Contusion	29	(18.2)	45	0	(0.0)	0
Shunt stenosis	26	(16.4)	44	0	(0.0)	0
Procedural hypotension	8	(5.0)	13	0	(0.0)	0

[†]MedDRA ver. 19.1J. SS, Safety analysis set.

level (n = 13), increase of Hb level (n = 10), consent withdrawn (n = 3), protocol violation (n = 2), and others (n = 11) (Fig. 1). Patient characteristics and baseline of the variables are presented in Table 2. Among the 159 patients that entered the treatment period, 56 patients received weekly darbepoetin alfa, five received biweekly darbepoetin alfa, and 96 received rHuEPO during the observation period (Table 2). The mean ± SD baseline Hb level was 10.88 ± 0.51 g/dL, and the range was 9.5–-12.2 g/dL. The mean ± SD duration of treatment with JR-131 was 297.2 ± 113.9 days (range, 1–359 days). The usage rate of iron preparations and iron-containing phosphate binders during the study did not change (Fig. S1 and Fig. S2, Supporting information).

Safety

The overall incidence of any TEAEs was 92.5% (147/159) and adverse drug reactions (ADRs) were 2.5% (4/159) (Table 3). TEAEs with a frequency ≥ 5% were nasopharyngitis (61.0%), contusion (18.2%), shunt stenosis (16.4%), diarrhea (15.7%), vomiting (8.8%), pain in extremity (8.8%), excoriation (8.8%), back pain (8.2%), musculoskeletal pain (8.2%), arthralgia (7.5%), gastroenteritis (6.3%), pruritus (6.3%), loss of consciousness (5.0%), orthostatic hypotension (5.0%), subcutaneous hemorrhage (5.0%), and procedural hypotension (5.0%). The ADRs observed were decreased platelet count in three patients and hypertension in one patient, respectively. TEAEs were mild in 1027 events, moderate in 52 events, and severe in seven events. All the ADRs were mild. The incidences of TEAEs were 37.1% (59/159) in the period of week 0 to 4, 71.1% (113/159) in week 0 to 12, 75.7% (106/140) in week 12 to 24, 75.0% (99/132) in week 24 to 36, 78.4% (98/125) in week 36 to 48, and 51.3% (59/115) after week 48. High incidences were not observed during any specific period including the early treatment-initiation period. The incidence of TEAEs was not dependent on the JR-131 dose. The incidences in sex and age were 92.2% (106/115) in male and 93.2% (41/44) in female, and 97.2% (69/71) in <65 years and 88.6% (78/88) in ≥65 years. The incidences in darbepoetin alfa were 93.4% (57/61) and in rHuEPO were 91.8% (90/98). The incidence of TEAEs did not have a specific tendency in any subgroup. Three deaths occurred due to sudden death, cardiac death, and cerebral hemorrhage death, but these were not considered related to JR-131. Although serious TEAEs were observed in 33 (20.8%) patients excluding three deaths, any causal relationship with JR-131 was denied. TEAEs leading

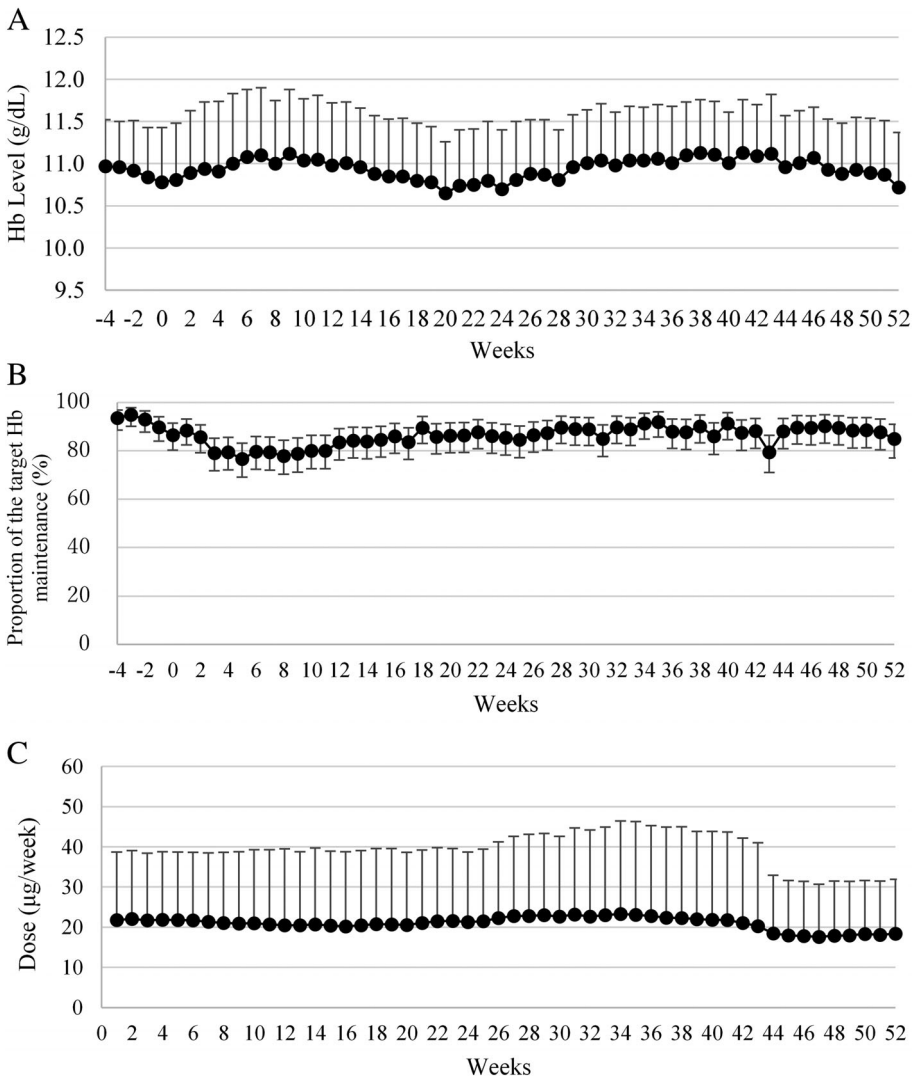

FIG. 2. Variables at each time point: (a) mean hemoglobin (Hb) level (standard deviation) (g/dL), (b) the proportion of the target Hb maintenance (95% confidence interval) (%), and (c) mean JR-131 dose (standard deviation) (μg/week).

to termination, discontinuation, and dose increase was present in nine patients (5.7%), one patient (0.6%), and three patients (1.9%), respectively. There were no TEAEs leading to dose reduction. No notable changes were observed in the laboratory tests (hematology, biochemistry, and iron parameters), vital signs, and weight throughout the study. An anti-JR-131 antibody was not detected.

Efficacy

The Hb level, the proportion of the target Hb maintenance, and the drug dose during each visit are shown in Figure 2. The mean ± SD Hb level at week 0, 12, 28, and 52 were 10.8 ± 0.7, 11.0 ± 0.7, 10.8 ± 0.6, and 10.7 ± 0.7 g/dL, respectively (Table S1). The baseline Hb level was in the range of 10.8–11.0 g/dL and the mean Hb levels during the treatment period were in the range of 10.7–11.1 g/dL, suggesting that the Hb levels were maintained within the target range of 10.0–12.0 g/dL throughout the study. The proportion of the target Hb maintenance at week 1, 12, 28, and 52 were 88.5%, 83.5%, 89.7%, and 85.0%, respectively. The proportion of the target Hb maintenance was 76.7–91.9% during the treatment period. The dose distribution at each visit is provided in Figure S2. About 80% of subjects received a dose of JR-131 up to 20 μg. The Hb levels in the subpopulations are shown in Figure 3. In patients receiving darbepoetin alfa during the observation period, no notable change in Hb level was observed during the treatment period, whereas the Hb levels in patients switching from rHuEPOs increased after starting treatment with JR-131. The Hb levels were recovered to the baseline level by dose adjustment in all subpopulations, and these

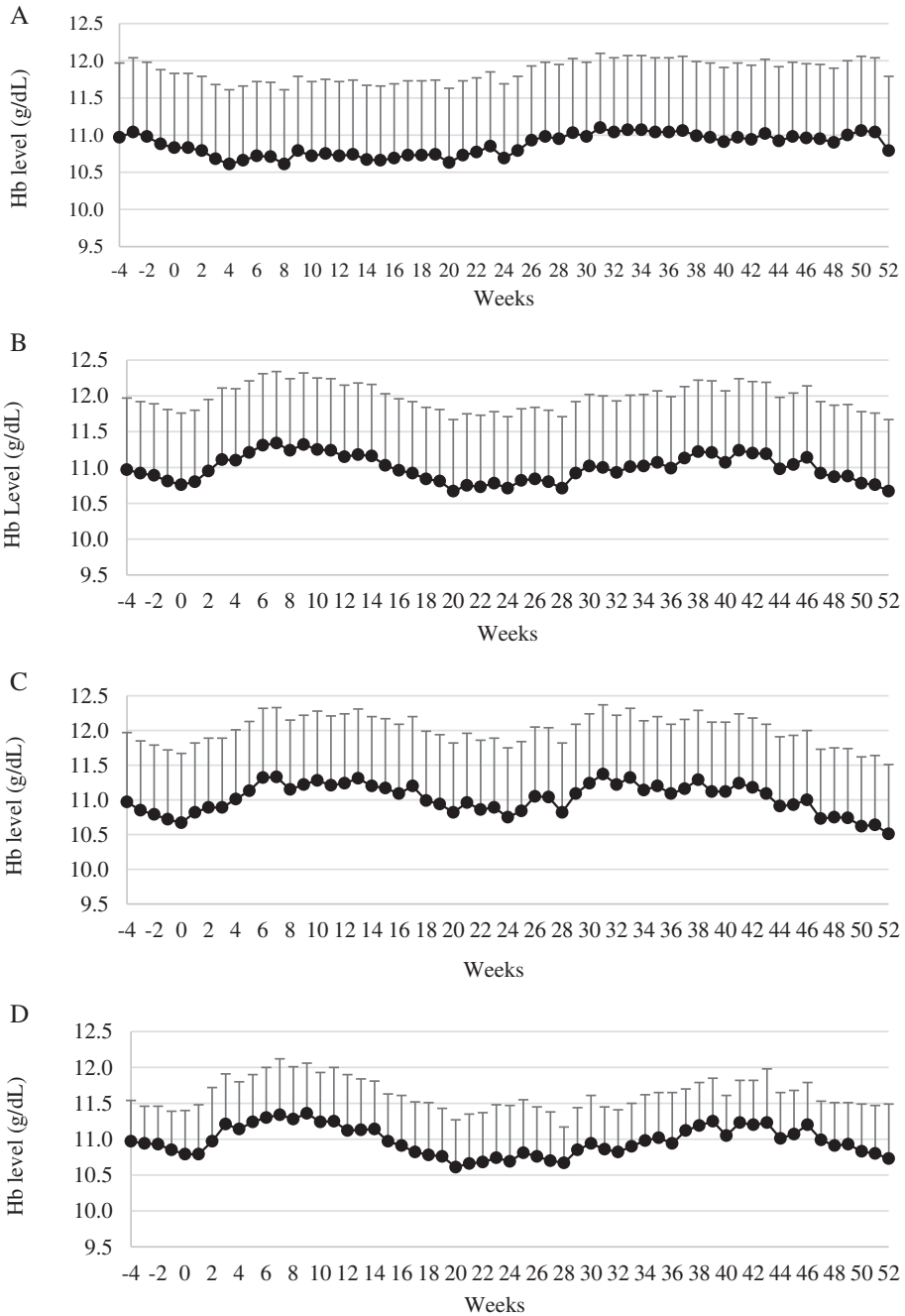

FIG. 3. Mean hemoglobin levels (standard deviation) at each time point in patients receiving: (A) darbepoetin alfa (n = 61), (B) all kind of recombinant human erythropoietins (n = 96), (C) epoetin beta (n = 28), and (D) epoetin kappa (n = 68) before switching to JR-131.

were maintained throughout the study. The observed mean dose conversion ratio ± SD for switching from rHuEPO to JR-131 was 203.6 ± 67.7 during the 4–8 weeks treatment period and 236.9 ± 83.2 during the all treatment period (Table 4).

DISCUSSION

This one-year study demonstrates that long-term treatment with JR-131 was safe, well-tolerated, and clinically useful in patients with renal anemia undergoing hemodialysis. JR-131 is a darbepoetin alfa biosimilar, which is an erythropoietin variant with a longer half-life. Renal anemia patients diagnosed with CKD and undergoing hemodialysis who received darbepoetin alfa or rHuEPOs such as epoetin alfa, beta, and kappa were enrolled in this study.

TEAEs and ADRs were reported in 92.5% (147/159) and 2.5% (4/159) of patients, respectively.

TABLE 4. *Observed dose conversion ratio for switching from rHuEPO to JR-131* (n = *96)*

rHuEPO dose at switching (IU/week)	Week	*N*	Mean ± SD	Min	Med	Max	95% CI
All	All	96	236.9 ± 83.2	52.3	231.0	440.6	[220.1, 253.8]
	4–8	93	203.6 ± 67.7	50.0	214.3	375.0	[189.7, 217.6]
1500	All	14	134.9 ± 56.2	52.3	130.5	266.0	[102.5, 167.3]
	4–8	14	102.1 ± 60.3	50.0	91.7	300.0	[67.3, 136.9]
2250	All	10	179.6 ± 44.3	101.7	179.6	231.7	[147.9, 211.3]
	4–8	10	161.5 ± 34.6	118.4	150.0	250.0	[136.7, 186.2]
3000	All	14	259.8 ± 74.8	179.3	234.6	440.6	[216.6, 303.0]
	4–8	13	221.0 ± 55.1	150.0	200.0	375.0	[187.7, 254.3]
3750	All	5	289.1 ± 27.5	243.8	291.0	314.5	[254.9, 323.2]
	4–8	5	214.4 ± 33.1	187.5	208.3	267.9	[173.3, 255.4]
4500	All	23	282.8 ± 85.3	131.5	280.2	410.5	[245.9, 319.7]
	4–8	22	248.0 ± 50.4	140.6	225.0	346.2	[225.6, 270.3]
6000	All	18	256.3 ± 53.5	192.0	246.1	378.2	[229.7, 282.9]
	4–8	18	220.9 ± 40.7	150.0	214.3	320.0	[200.7, 241.2]
7500	All	2	254.1 ± 29.1	233.5	254.1	274.6	[−7.12, 515.3]
	4–8	2	218.8 ± 44.2	187.5	218.8	250.0	[−178.3, 615.8]
9000	All	10	235.1 ± 80.5	123.2	230.3	346.7	[177.6, 292.7]
	4–8	9	231.2 ± 45.8	180.0	225.0	346.2	[196.0, 266.4]

CI, confidence interval; IU, international unit; Max, maximum; Med, median; Min, minimum; rHuEPO, recombinant human erythropoietin; SD, standard deviation.

The most common TEAEs with a frequency of ≥5% occurred incidentally and were common adverse events observed in hemodialysis patients (14). ADRs were decreased platelet count in three patients and hypertension in one patient. The severity of all the ADRs was mild. Onset time of TEAEs and ADRs were almost constant throughout the treatment period. There were no TEAEs that occurred at any specific period with high incidence, and no significant TEAEs were seen in this long-term treatment with JR-131. Compared with the results of the previous phase 3 trial (21), our results confirmed similarity between JR-131 and the ADRs in the package insert of darbepoetin alfa (13). No notable TEAEs occurred at the specified dose. There was no notable trend in the occurrence of any specific TEAE concerning demographic characteristics including sex, age (<65 years/≥65 years), and treatment for renal anemia during the observation period with ESAs (darbepoetin alfa, rHuEPO including epoetin beta and kappa). An anti-JR-131 antibody was not detected in this study.

The mean Hb level during the treatment period (week 1 to week 52) remained within the target range of ≥10.0 g/dL to <12.0 g/dL, which is the recommended Hb level by the 2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease (6). The mean weekly dose of JR-131 was 17.6 to 23.3 μg, and large variation was not found. The proportions of the target Hb maintenance were 76.7–91.9% in every week assessment during the treatment period. The proportions of the target Hb maintenance decreased after starting the treatment with JR-131. Although the dose of ESA for treating renal anemia is generally adjusted to maintain the target Hb level (6), the protocol of this study did not allow dose adjustment of ESAs during the observation period and the first 2 weeks after switching to JR-131, for a total of 6 weeks. No chance of dose adjustment might lead to a temporary decrease in the proportions of the target Hb maintenance at the beginning of the study. After dose adjustment, the proportions of the target Hb maintenance increased. In the study subpopulations in whom rHuEPO was switched to JR-131, the Hb levels increased gradually after starting treatment with JR-131. Dose conversion from rHuEPO to JR-131 was made according to the dose conversion table from rHuEPO to JR-131, which was designed based on the 1: 200 conversion ratio rule. However, several reports described that this ratio overestimated the adequate dose of darbepoetin alfa (15). Bock et al. reported that the actual conversion ratio was 1:336 in a 24-week treatment (16). The dose conversion ratio for Japanese hemodialysis patients with renal anemia was reported to be 1:350.5 in a 24-week study (17), and 1:286.6 in a 52-week study (18). These suggested that the initial Hb increase when switching from rHuEPO to JR-131 was due to an overestimated dose conversion. After dose was adjusted based on the Hb level from 2 weeks after switching to JR-131, the Hb was recovered to a baseline level. Additionally, the observed mean ± SD conversion ratios from rHuEPO to JR-131 in this study were 203.6 ± 67.7 (95% CI, 189.7–217.6) during the early treatment period (week 4 to week 8), and 236.9 ± 83.2 (95% CI, 220.1–253.8) during the total treatment period.

These results suggest that JR-131 can be used to manage renal anemia in patients undergoing hemodialysis with individual dose adjustment when switching from rHuEPO to JR-131 as well as darbepoetin alfa. Although the number of patients switching from biweekly darbepoetin alfa to JR-131 was limited, no trend was observed in the dose and Hb level.

Woodland et al., demonstrated favorable cost-effectiveness of darbepoetin alfa over rHuEPOs for renal anemia management in patients undergoing hemodialysis (19). Nakagawa reported that darbepoetin alfa was more cost-effective than epoetin alfa in the treatment of renal anemia in Japanese patients undergoing hemodialysis (20). Among ESAs, darbepoetin alfa is the most common ESAs in Japan due to its less frequent administration than the epoetins and its cost-effectiveness (11). Dialysis patients receiving ESAs require lifelong management of renal anemia. The number of dialysis patients in Japan continues to increase every year; at the end of 2016, the number has reached 329 609 (8). Although the cost of ESAs is bundled with other dialysis charges, the introduction of a lower-cost of darbepoetin alfa biosimilar is needed to reduce dialysis expenditures (9). Therefore, JR-131, a darbepoetin alfa biosimilar, demonstrated long-term safety and efficacy, suggesting a significant contribution to our healthcare system.

There are, however, some limitations in this study. First, this study was a single-arm setting; there was no comparator. The phase 3 study revealed JR-131 was clinically comparable to darbepoetin alfa. Second, the duration of this long-term study was 52 weeks; the use of ESAs for the treatment of dialysis patients with renal anemia is lifelong. More extended studies on the safety and effectiveness are needed during post-marketing surveillance.

CONCLUSION

JR-131 showed favorable safety profiles during the 52-week treatment. JR-131 maintained hemoglobin levels in patients with chronic kidney disease undergoing hemodialysis without clinically significant adverse events. No patients developed anti-JR-131 antibodies. Therefore, JR-131 is a useful and cost-effective darbepoetin alfa alternative in the management of renal anemia in patients undergoing hemodialysis.

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Conflict of Interest: Shinichi Nishi, Kazuhiko Tsuruya, Ikuto Masakane, and Hidetomo Nakamoto are advisers to JCR Pharmaceuticals and Kissei Pharmaceutical. Shinichi Nishi reports receiving lecture fee from Kyowa Hakko Kirin Pharmaceutical. Kazuhiko Tsuruya, Ikuto Masakane, and Hidetomo Nakamoto report receiving lecture fee and grant from Kyowa Hakko Kirin Pharmaceutical and Chugai Pharmaceutical. Masayuki Yamada an is employee of Kissei Pharmaceutical.

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SUPPORTING INFORMATION

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TABLE S1. Hemoglobin level (g/dL) at each visit during the study (FAS)

Fig. S1. Proportion of use of iron preparation (FAS).

Fig. S2. Proportion of use of iron-containing phosphate binders (FAS).

Fig. S3. Dose distribution of JR-131 (FAS).