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JR-131, a Biosimilar of Darbepoetin Alfa, for the Treatment of Hemodialysis Patients With Renal Anemia: A Randomized, Double-Blinded, Parallel-Group Phase 3 Study

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Abstract: The aim of this study was to compare the efficacy and safety of intravenous JR-131, a darbepoetin alfa biosimilar, to darbepoetin alfa in hemodialysis patients with renal anemia. In this 24-week, multicenter, randomized, double-blinded, parallel-group phase 3 study, 334 hemodialysis patients with renal anemia who had been receiving darbepoetin alfa were randomized to either JR-131 or darbepoetin alfa group. The initial dose was set based on the darbepoetin alfa dose during the observation period. The primary endpoint was change in hemoglobin level from baseline to end of treatment. The 95% confidence interval of the difference in the change in hemoglobin level between the groups was −0.19 to −0.20 g/dL, within the equivalent margin of −0.5 to 0.5 g/dL. No notable treatment-emergent adverse events were observed in either group. JR-131 was therapeutically equivalent to darbepoetin alfa, and the safety profile of JR-131 was similar to that of darbepoetin alfa.
Key Words: Biosimilar, Darbepoetin alfa, Erythropoiesis-stimulating agent, JR-131, Renal anemia.

Renal anemia is a common complication in patients with chronic kidney disease (CKD), progressing exponentially with decline in kidney function due to insufficient erythropoietin production in the kidney (1). Renal anemia in patients with CKD, particularly those undergoing hemodialysis, is associated with an increased risk of decreased quality of life, hospitalization, cardiac morbidity, and all-cause mortality (2–4). The remedy for renal anemia over the last two decades has been erythrocyte transfusion, iron preparation, and erythropoiesis-stimulating agents (ESAs) (5–7). Among them, ESAs are used in almost 90% of dialysis patients in Japan (8), and five ESAs, epoetin alfa, epoetin beta, epoetin kappa, darbepoetin alfa, and epoetin beta pegol, are currently available.

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Dialysis patients receiving ESAs require lifelong use, and the number of chronic dialysis patients in Japan continues to increase every year; it reached 329 609 at the end of 2016 (9). Although the cost of ESAs is included in bundled payment for dialysis treatment, introduction of a lower-cost ESA biosimilar is desirable to reduce dialysis expenditures (10). Epoetin kappa, a biosimilar of epoetin alfa developed by JCR Pharmaceuticals (Ashiya, Hyogo Prefecture, Japan) and Kissei Pharmaceutical (Matsumoto, Nagano Prefecture, Japan), was approved in 2010 as the sole biosimilar of ESAs in Japan (11). However, among ESAs, darbepoetin alfa has been the most common ESA in Japan to date because of its less frequent administration than the epoetins.

JR-131 is the first domestically produced biosimilar of darbepoetin alfa, a long-acting ESA developed by JCR Pharmaceuticals and Kissei Pharmaceutical. JR-131 is produced by recombinant DNA technology in completely serum-free medium without the use of any animal-derived materials. The development strategy was planned in accordance with the Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics issued 2009 by the Japanese regulatory

authority (12). The quality of JR-131 was confirmed to be identical/similar to that of the reference product, darbepoetin alfa. Preclinical comparative studies on the pharmacology, pharmacokinetics, and toxicology of JR-131 revealed similarities to darbepoetin alfa. In phase 1 clinical trials in healthy Japanese male volunteers, the safety, tolerability, and pharmacokinetics of JR-131 were similar/equivalent to those of darbepoetin alfa, when administered either intravenously or subcutaneously. The aim of this phase 3 study was to evaluate the therapeutic equivalence of JR-131 to darbepoetin alfa in hemodialysis patients with renal anemia.

PATIENTS AND METHODS

Study design and patients

This was a multicenter, randomized, double-blinded, parallel-group, active-controlled phase 3 study in hemodialysis patients with renal anemia. The study was conducted at 33 sites in Japan from September 2016 to September 2017. The study protocol and the informed consent form were approved by the institutional review board at each participating study site. All patients gave written informed consent before initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines. This study is registered in ClinicalTrials.gov.: NCT02912494.

Male or female patients aged ≥20 years with CKD who were diagnosed with renal anemia were enrolled in this study. The inclusion criteria were patients undergoing maintenance dialysis including hemodialysis or hemodiafiltration three times a week for ≥12 weeks before start of the observation period, patients receiving a constant dose and regimen of intravenous darbepoetin alfa once a week for ≥4 weeks, and patients with a hemoglobin (Hb) level of 9.5 to 12.5 g/dL measured before the first dialysis of the week for ≥4 weeks. Other inclusion criteria were a mean Hb level of ≥10.0 to <12.0 g/dL with a variation of not more than 1.5 g/dL measured before the first dialysis of the week during the observation period, a transferrin saturation (TSAT) ≥20% or ferritin level ≥ 100 ng/mL at start of the observation period, and maintenance of dialysis conditions including frequency and method of dialysis throughout the study. Key exclusion criteria were barely controllable hypertension (1/3 or more of diastolic blood pressure measurements before dialysis during 12 weeks before the start of observation period ≥100 mmHg); 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 start of observation period; or ESAs other than darbepoetin alfa, a protein anabolic hormone, testosterone enanthate, mepitiostane, levocarnitine, a zinc-containing preparation, a copper-containing preparation, an oral iron preparation, or an iron-containing phosphate binder during 16 weeks before start of the observation period. This study consisted of a 4-week observation period and a 24-week treatment period. Patients who met the eligibility criteria entered a 4-week observation period. During this observation period, subjects received darbepoetin alfa (Nesp, Kyowa Hakko Kirin, Tokyo, Japan) intravenously once a week at end of the first dialysis of the week for 4 weeks. Changes in the dose and regimen of darbepoetin alfa during the observation period were not allowed. Subjects were randomly assigned in a 1:1 ratio to receive either JR-131 or darbepoetin alfa by the Interactive Web Response System of an independent organization using a dynamic allocation method with the following darbepoetin alfa doses at start of the observation period: 5 to 20 μg, 30 to 60 μg, and 80 to 180 μg as a stratification factor. The initial dose was set according to the dose of darbepoetin alfa during the observation period. The assigned study drug was administered intravenously once a week at end of the first dialysis of the week for 24 weeks. Prefilled syringes of darbepoetin alfa were purchased, and the corresponding prefilled syringes of JR-131 were prepared by the sponsor. To maintain blinding of the patient and assessor, the study drug was administered by other un-blinded study staff. The investigator adjusted the dose to maintain the Hb level in the target range of ≥10.0 to <12.0 g/dL in accordance with the table of dose change and adjustment criteria (Table 1). A one-step increase or decrease in the dose was allowed. A dose change of two steps or more from the initial dose was not allowed, nor was a dose change within 2 weeks. In the case of an treatment-emergent adverse event (TEAE), dose maintenance or cessation of the study drug was allowed at the discretion of the investigator. Administration of the same dose was continued to the next week when the Hb level in two consecutive measurements was ≥12.0 to <12.5 g/dL after dose reduction or at the minimum dose (5 μg), >9.0 to <9.5 g/dL after a dose increase or at the maximum dose (180 μg), or the two consecutive change in Hb level from baseline was > +1.0 g/dL after dose reduction or at the minimum dose (5 μg), or the two consecutive change in Hb level from baseline was < −1.0 g/dL after dose increase or at the maximum dose (180 μg). The baseline Hb level was defined as the mean Hb level at

TABLE 1. *Dose change and adjustment criteria*

Evaluation item	Variable	Dose adjustment
Hemoglobin level	≥9.5 to <12.0 g/dL	Maintain
	≥12.0 g/dL*	1-step reduction
	<9.5 g/dL*	1-step increase
Change from the baseline hemoglobin level	± 1.0 g/dL	Maintain
	>1.0 g/dL*	1-step reduction
	<−1.0 g/dL*	1-step increase
Dose adjustment	Step 1	5 μg
	Step 2	10 μg
	Step 3	15 μg
	Step 4	20 μg
	Step 5	30 μg
	Step 6	40 μg
	Step 7	50 μg
	Step 8	60 μg
	Step 9	80 μg
	Step 10	100 μg
	Step 11	120 μg
	Step 12	140 μg
	Step 13	160 μg
	Step 14	180 μg

*Two consecutive measured levels of hemoglobin.

Week −3, −2, −1, and 0 of the observation period. During the treatment period, a change in the administration regimen of the study drug was not allowed. When the Hb level in two consecutive measurements was <9.0 or >12.5 g/dL, patients were withdrawn from the study. Other withdrawal criteria related to Hb levels were Hb ≥ 12.0 g/dL in four consecutive measurements at the minimum dose (5 μg) or after dose reduction; Hb < 9.5 g/dL at the maximum dose (180 μg) or after a dose increase; a change in the Hb level from baseline in four consecutive measurements of ≥ +1.0 g/L at the minimum dose (5 μg) or after dose reduction; or a change in the Hb level from baseline of < −1.0 g/dL at the maximum dose (180 μg) or after a dose increase. Administration of an intravenous iron preparation was allowed as a guide for TSAT <20% and/or ferritin <100 ng/mL. Medication with ESAs other than darbepoetin alfa, a protein anabolic hormone, testosterone enanthate, mepitiostane, levocarnitine, a zinc-containing preparation, a copper-containing preparation, an oral iron preparation, an iron-containing phosphate binder, or any investigational product other than JR-131, and erythrocyte transfusion were prohibited throughout the study.

Efficacy and safety assessments

At the first dialysis of the week, the Hb level and study drug dose were assessed. The primary endpoint was a change in the Hb level from baseline to end of the treatment. The Hb level at end of treatment was defined as the mean Hb level at Week 21, 22, 23, and 24. In the subjects who discontinued the study, the mean Hb level of the last 4 weeks measured before discontinuation was used as the Hb level at end of the treatment. Secondary endpoints were the Hb level at each time point, proportion of subjects who maintained the baseline Hb level, dose at each time point, total dose, and proportional change in the dose. Safety was assessed according to 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). Anti-drug antibody (anti-JR-131 antibody and anti- darbepoetin alfa antibody) were tested using a blood sample by electrochemiluminescence (ECL) at Week 0 and 24, and if positive, the neutralizing antibody was tested.

Statistical analysis

The sample size was calculated based on the assumption that an equivalent margin in the primary endpoint was set to −0.5 to 0.5 g/dL, differences in Hb level between the groups was 0 g/dL, and the standard deviation (SD) was 0.9 g/dL. We calculated that a sample size of 86 randomly assigned patients in each group would be sufficient to provide 90% power with a two-sided 5% significance level. The same equivalence margin was used previously for a comparability study of epoetin kappa and epoetin alfa (12,13).

Safety analysis was performed for subjects in the safety set (SS), and efficacy was analyzed primarily for the full analysis set (FAS) and secondarily in the per-protocol set (PPS). The SS consisted of subjects excluding those who were GCP non-compliant, those who did not receive the study drug, and those who discontinued the study before treatment initiation. The FAS included the SS subjects excluding those who had no primary data-assessment endpoint. The PPS was defined as the subset of subjects in the FAS excluding those who did not meet the eligibility criteria, those who discontinued the study treatment before 16 weeks, those who deviated substantially from the protocol, and those whose emergency key was opened.

Continuous variables were summarized as mean, SD, two-sided 95% confidence interval (CI), minimum, median, and maximum, and categorical data as percentage.

For the primary endpoint, the difference in mean changes between the groups and two-sided 95% CI in the Hb level from baseline to end of the treatment were calculated. In a case wherein the 95% CI was in the range of −0.5 g/dL to 0.5 g/dL, it was determined that the equivalence of JR-131 to darbepoetin alfa would be verified. For sensitivity

analysis, the primary endpoint was also evaluated in the PPS population and evaluated by analysis of covariance (ANCOVA) using the group as the fixed effect and darbepoetin alfa dose during the observation period as the covariate. The primary endpoint was also evaluated in the subpopulation including sex (male and female) and age (<65 years and ≥65 years). For secondary endpoints, the Hb levels, dose, and change in Hb levels from baseline at each time point by group were summarized. Subjects whose change in Hb level from baseline was in the range of ±1.0 g/dL were defined as those who maintained the baseline Hb levels. The proportion of subjects who maintained the baseline Hb level by group at each time point was summarized. Summary statistics for the mean total dose and difference in the total dose between the groups were calculated.

For safety assessment, events that occurred after administration of the study drug were analyzed TEAEs. The number of TEAEs or adverse drug reactions (ADRs), which were TEAEs related to the study drug that occurred, number of subjects who experienced TEAEs were shown by group. The difference in TEAEs and ADRs between the groups were analyzed by the Fisher's exact test. TEAEs were coded using the Medical Dictionary for Regulatory Activities ver. 19.1.

All statistical tests were performed using a two-sided significance level of 0.05. All analyses were performed using SAS software ver. 9.4 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

A total of 355 patients were enrolled and 334 were randomly assigned to either the JR-131 (n = 171) or darbepoetin alfa groups (n = 163) (Fig. 1). Among them, 116 and 115 subjects entered the treatment period in the JR-131 and darbepoetin alfa groups, respectively. The FAS population was 223 after excluding eight subjects (JR-131 group: five subjects, darbepoetin alfa group: three subjects) from the SS because they had no data for assessing the primary

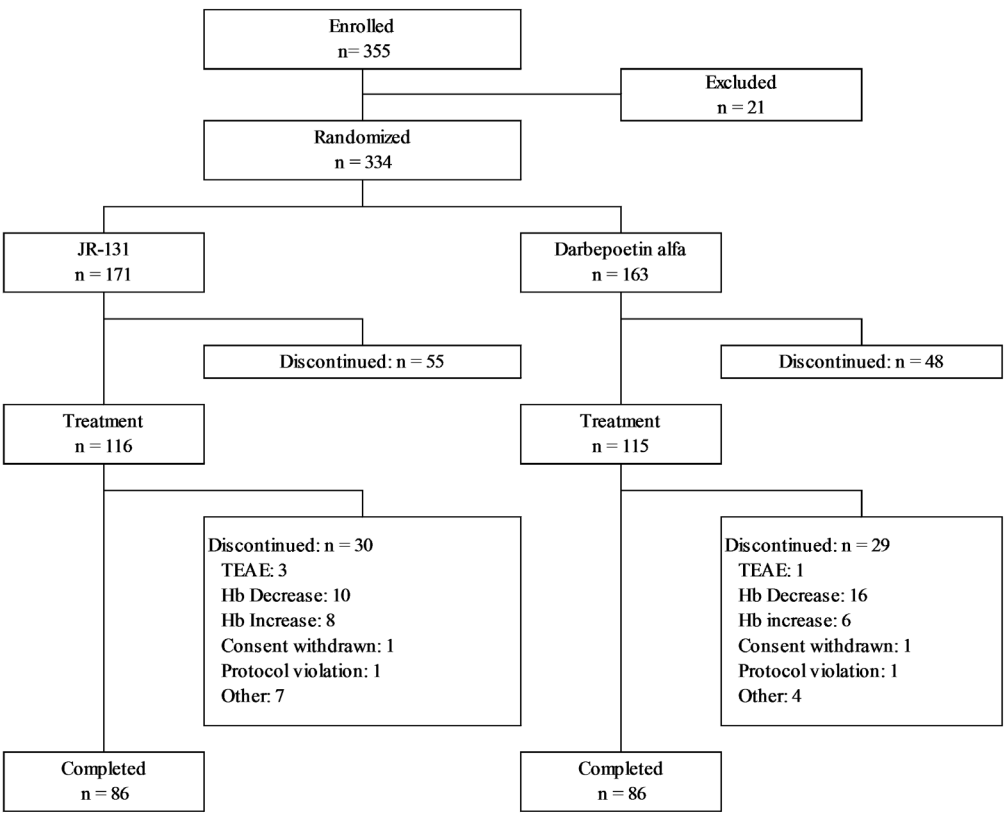

FIG. 1. Patient disposition.

TABLE 2. *Patient baseline characteristics (FAS)*

	JR-131 *n* = 111	Darbepoetin alfa *n* = 112
Sex		
Male, *n* (%)	78 (70.3)	78 (69.6)
Female, *n* (%)	33 (29.7)	34 (30.4)
Age (years)		
Mean ± SD (Min, Med, Max)	67.3 ± 12.1 (32, 69, 88)	67.5 ± 9.6 (37, 69, 89)
<65, *n* (%)	39 (35.1)	34 (30.4)
≥65, *n* (%)	72 (64.9)	78 (69.6)
Dry weight (kg)		
Mean ± SD (Min, Med, Max)	55.58 ± 10.93 (34.9, 54.4, 95.7)	58.05 ± 11.87 (36.0, 56.8, 104.8)
Primary cause CKD (overlapping), *n*		
Diabetic kidney disease	35	40
Chronic glomerulonephritis	31	35
Nephrosclerosis	21	17
Polycystic kidney disease	3	7
Chronic pyelonephritis	0	0
Others	8	8
Unknown	13	7
Method of dialysis		
Hemodialysis, *n* (%)	93 (83.8)	92 (82.1)
Hemodiafiltration, *n* (%)	18 (16.2)	20 (17.9)
Duration of dialysis (months)		
Mean ± SD (Min, Med, Max)	86.6 ± 69.8 (4, 65, 323)	94.9 ± 93.7 (6, 60, 453)
Darbepoetin alfa dose (μg) during the observation phase		
Mean ± SD (Min, Med, Max)	18.6 ± 14.7 (5, 15, 120)	18.2 ± 14.7 (5, 15, 120)
5–20 μg, *n* (%)	88 (79.3)	88 (78.6)
30–60 μg, *n* (%)	22 (19.8)	23 (20.5)
80–180 μg, *n* (%)	1 (0.9)	1 (0.9)
Hemoglobin (g/dL)		
Mean ± SD (Min, Med, Max)	11.0 ± 0.6 (9.8, 11.0, 12.0)	11.0 ± 0.5 (9.9, 11.0, 12.0)
Ferritin (μg/L)		
Mean ± SD (Min, Med, Max)	137.1 ± 139.7 (9.0, 80.1, 939.0)	129.9 ± 142.8 (10.2, 103.0, 1310.0)
Transferrin saturation (%)		
Mean ± SD (Min, Med, Max)	28.0 ± 11.1 (7.4, 27.6, 89.1)	25.8 ± 9.0 (6.8, 24.1, 56.0)

CKD, chronic kidney disease; FAS, full analysis set; Max, maximum; Med, median; Min, minimum; SD, standard deviation.

endpoint. Patients' characteristics in the FAS population were similar across treatment groups (Table 2). During the observation period, there was no difference in the dose and baseline Hb level between the groups. Notable differences between the groups were not found in the dose distributions of the study drug and use of intravenous iron preparations throughout the study (Figs S1,S2).

Efficacy

For the primary endpoint, the mean changes ± SD (95% CI) in Hb level from baseline to end of treatment without adjustment were −0.42 ± 0.73 (−0.56, −0.29) g/dL in the JR-131 group and − 0.43 ± 0.77 (−0.57, −0.28) g/dL in the darbepoetin alfa group (Table 3). The difference (95% CI) in the mean changes in Hb level between the groups was 0.01 (−0.19, 0.20) g/dL, which was within the equivalent margin of −0.5 to 0.5 g/dL. This indicated equivalence of JR-131 to darbepoetin alfa in the primary endpoint. Also, in the PPS population and ANCOVA method, the equivalences between the groups were confirmed. Similar results were obtained in the analysis by subpopulation, including sex (male and female), and age (<65 years and

TABLE 3. *Change in hemoglobin level (g/dL) from baseline to end of treatment (FAS)*

Hemoglobin level (g/dL)	JR-131 *N* = 111			Darbepoetin alfa *N* = 112		
	Mean ± SD	Min, Med, Max	95% CI	Mean ± SD	Min, Med, Max	95% CI
Baseline	11.03 ± 0.57	9.8, 11.0, 12.0	10.93, 11.14	10.99 ± 0.52	9.9, 11.0, 12.0	10.89, 11.08
End of treatment	10.61 ± 0.79	8.6, 10.6, 12.5	10.46, 10.76	10.56 ± 0.86	8.7, 10.5, 12.6	10.40, 10.72
Change from baseline to end of treatment	−0.42 ± 0.73	−3.4, −0.4, 1.3	−0.56, -0.29	−0.43 ± 0.77	−2.1, −0.4, 2.0	−0.57, -0.28
The difference of mean changes between the groups	0.01 95% CI [−0.19, 0.20]					

CI, confidence interval; Max, maximum; Med, median; Min, minimum; SD, standard deviation.

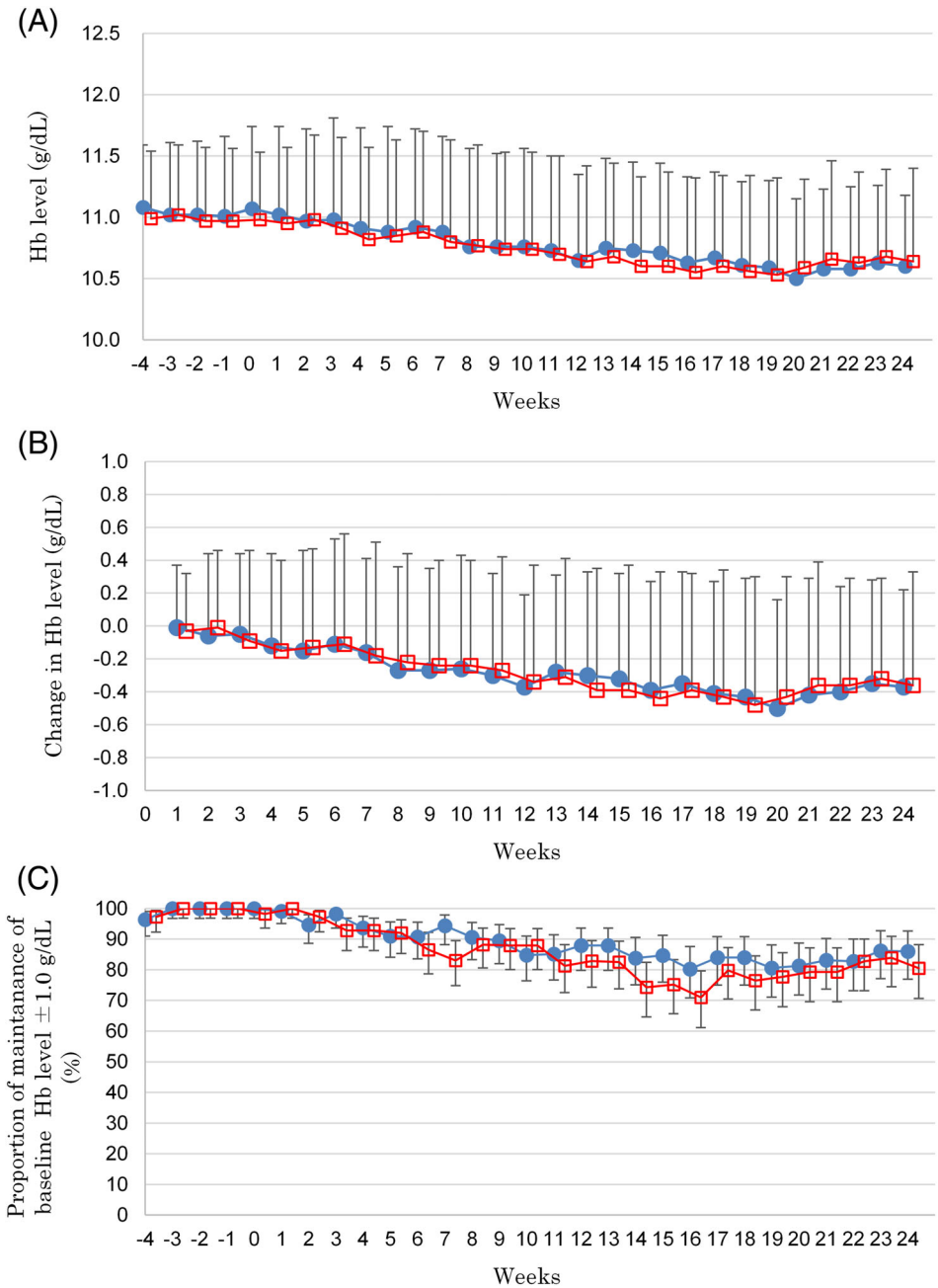

FIG. 2. The mean and standard deviation of hemoglobin level (g/dL) at each visit (A), the mean change and standard deviation of hemoglobin level (g/dL) from baseline to each visit (B), and the proportion (95% confidence interval) of maintenance of the baseline hemoglobin level (g/dL) at each visit (C). —●— JR-131, —□— Darbepoetin. [Color figure can be viewed at wileyonlinelibrary.com]

≥65 years). The Hb levels and change in Hb levels at each time point remained relatively steady throughout the treatment period, and there was no difference between the groups (Fig. 2a,b). Change in the maintenance rate of baseline Hb level within ±1.0 g/dL is presented in Figure 2c. The proportions of maintenance of the baseline Hb level in the JR-131 and darbepoetin alfa groups were 80.2% to 99.1% and 71.0% to 100.0%, and no significant difference was observed between the groups. The doses were kept relatively steady throughout the treatment period, and there was no significant difference between the groups (Fig. 3).

The mean total administered doses ± SD of JR-131 and darbepoetin alfa were 411.1 ± 352.5 μg (95% CI, 344.8, 477.4) and 386.5 ± 255.6 μg (95% CI, 338.7, 434.4), respectively (Table 4). The mean difference in the total administered doses between the groups was 24.6 μg (95% CI, −56.6, 105.8), suggesting no significant difference between the groups. As to the change in dose during the treatment period, no relative difference was found

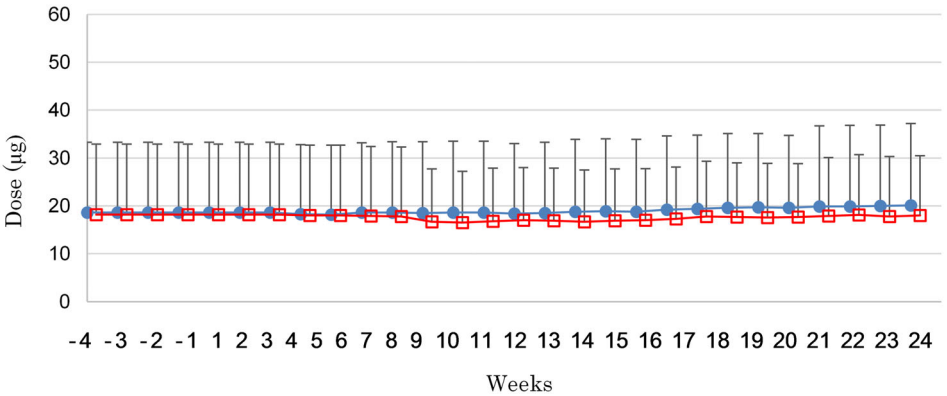

FIG. 3. The mean dose and standard deviation of the study drug at each visit. During the observation phase (Week −4 to Week −1), darbepoetin alfa was administered. The first administration week of the study drug was presented as Week 1. JR-131, Darbepoetin. [Color figure can beviewed at wileyonlinelibrary.com]

between the groups (Table 4). The proportions of subjects whose baseline dose was maintained during the study were 53.2% in the JR-131 group and 48.2% in the darbepoetin alfa group. The dose increases from baseline in the JR-131 and darbepoetin alfa groups were 27.0% and 30.4%, and the dose reductions were 18.0% and 16.1%, respectively. In 1.8% of subjects in the JR-131 group and 5.4% in the darbepoetin alfa group, dose increase and reduction were performed.

Safety

The overall incidences of any TEAEs were 82.8% (96/116) in the JR-131 group and 87.0% (100/115) in the darbepoetin alfa group (P = 0.463). The difference in incidence of TEAEs between the groups was −4.2% (95% CI, −13.4, 5.0). The incidence of ADRs were 1.7% (2/116) in the JR-131 group and 0.9% (1/115) in the darbepoetin alfa group (P = 1.000), and the difference between the groups was 0.9% (95% CI, −2.1, 3.8). TEAEs with a frequency ≥ 5% in any group were nasopharyngitis, shunt stenosis, vomiting, diarrhea, procedural hypotension, excoriation, back pain, contusion, and upper respiratory tract inflammation (Table 5). ADRs observed in the JR-131 group were aspartate aminotransferase increased (n = 1) and blood creatine phosphokinase increased (n = 1), and in the darbepoetin alfa group was hypertension (n = 1). Almost all TEAEs were mild or moderate in intensity, 300 and 321 events were graded as mild, 30 and 22 events moderate in the JR-131 and darbepoetin alfa groups, respectively. The severity of all ADRs was mild. Severe adverse events in the JR-131 and darbepoetin alfa groups were aortic aneurysm rupture (n = 1) and cholecystitis (n = 1), respectively. The aortic aneurysm rupture reported in the JR-131 group led to death. However, causality of the study drug in these severe adverse events was denied. Serious adverse events (SAEs) excluding death occurred in 14 subjects in the JR-131 group and 12 in the darbepoetin alfa group. None of the SAEs were considered related to the study drugs. TEAEs leading to discontinuation of the study treatment occurred in three subjects in the JR-131 group and in one subject in the darbepoetin alfa group. TEAE leading to interruption was hypertension in one subject of the darbepoetin alfa group. Causality of the study drug were denied except in the case of hypertension. There was no TEAE leading to a dose reduction. No notable changes in clinical laboratory tests, vital signs, and weight were observed during the study. Anti-JR-131 antibody and anti-darbepoetin alfa antibody were not detected.

TABLE 4. *Total administered dose and summary of dose change during the study (FAS)*

	JR-131 N = 111	Darbepoetin alfa N = 112
Total dose of administration (μg)		
Mean ± SD	411.1 ± 352.5	386.5 ± 255.6
95% CI	[344.8, 477.4]	[338.7, 434.4]
Min, Med, Max	25, 360, 2960	65, 325, 1410
Mean difference between the groups (μg)	24.6	
95% CI	[−56.6, 105.8]	
Dose change during the study, n (%)		
No	59 (53.2)	54 (48.2)
Increase	30 (27.0)	34 (30.4)
Reduce	20 (18.0)	18 (16.1)
Increase and reduce	2 (1.8)	6 (5.4)

CI, confidence interval; Max, maximum; Med, median; Min, minimum; SD, standard deviation.

DISCUSSION

This phase 3 study revealed that JR-131 was clinically useful and safe for the treatment of hemodialysis patients with renal anemia, as well as darbepoetin alfa as its biosimilar. In this study, patients undergoing maintenance hemodialysis who received a stable dose of darbepoetin alfa were randomly assigned to

TABLE 5. *Most common treatment-emergent adverse events (preferred term incidence ≥5% in either group) and adverse drug reactions (SS)**

Primary system organ class	Treatment-emergent adverse events						Adverse drug reactions					
	JR-131 N = 116			Darbepoetin alfa N = 115			JR-131 N = 116			Darbepoetin alfa N = 115		
Preferred term	*n*	(%)	Events	*n*	(%)	Events	*n*	(%)	Events	*n*	(%)	Events
All	96	(82.8)	331	100	(87.0)	344	2	(1.7)	2	1	(0.9)	1
Infections and infestations	47	(40.5)	62	54	(47.0)	73	0	(0.0)	0	0	(0.0)	0
Nasopharyngitis	34	(29.3)	42	33	(28.7)	43	0	(0.0)	0	0	(0.0)	0
Vascular disorders	5	(4.3)	6	8	(7.0)	8	0	(0.0)	0	1	(0.9)	1
Hypertension	1	(0.9)	1	3	(2.6)	3	0	(0.0)	0	1	(0.9)	1
Respiratory, thoracic, and mediastinal disorders	11	(9.5)	11	21	(18.3)	24	0	(0.0)	0	0	(0.0)	0
Upper respiratory tract inflammation	3	(2.6)	3	12	(10.4)	13	0	(0.0)	0	0	(0.0)	0
Gastrointestinal disorders	40	(34.5)	67	37	(32.2)	54	0	(0.0)	0	0	(0.0)	0
Diarrhea	9	(7.8)	13	5	(4.3)	6	0	(0.0)	0	0	(0.0)	0
Vomiting	12	(10.3)	16	8	(7.0)	10	0	(0.0)	0	0	(0.0)	0
Musculoskeletal and connective tissue disorders	23	(19.8)	36	23	(20.0)	31	0	(0.0)	0	0	(0.0)	0
Back pain	6	(5.2)	7	7	(6.1)	8	0	(0.0)	0	0	(0.0)	0
Investigations	13	(11.2)	16	10	(8.7)	14	2	(1.7)	2	0	(0.0)	0
Aspartate aminotransferase increased	1	(0.9)	1	0	(0.0)	0	1	(0.9)	1	0	(0.0)	0
Blood creatine phosphokinase increased	5	(4.3)	5	2	(1.7)	2	1	(0.9)	1	0	(0.0)	0
Injury, poisoning and procedural complications	36	(31.0)	53	36	(31.3)	53	0	(0.0)	0	0	(0.0)	0
Excoriation	7	(6.0)	11	5	(4.3)	6	0	(0.0)	0	0	(0.0)	0
Contusion	5	(4.3)	5	9	(7.8)	10	0	(0.0)	0	0	(0.0)	0
Shunt stenosis	13	(11.2)	13	13	(11.3)	18	0	(0.0)	0	0	(0.0)	0
Procedural hypotension	8	(6.9)	10	2	(1.7)	2	0	(0.0)	0	0	(0.0)	0

*MedDRA ver. 19.1.

either JR-131 or darbepoetin alfa treatment groups. The study drug was administered intravenously once a week at end of the first dialysis of the week for 24 weeks. The efficacy of JR-131 was found to be equivalent to that of darbepoetin alfa according to the primary endpoint, which was evidenced by a change in the Hb level from baseline to end of treatment. Similar results were obtained in sensitivity analyses, indicating the robustness of the equivalence of efficacy between JR-131 and darbepoetin alfa. In all secondary endpoints, the Hb levels, changes in the Hb levels, proportions of maintenance of the baseline Hb levels, and doses at each time point were similar between the groups. Hb levels showed a tendency to decrease over time through the treatment period, but there was no difference between the groups. The aim of our study was to confirm the therapeutic equivalence of JR-131 and darbepoetin alfa. Therefore, strict dose change and adjustment criteria were maintained in our study. As results, the mean change ± SD in Hb levels from baseline to end of treatment was −0.42 ± 0.73 g/dL in the JR-131 group and −0.43 ± 0.77 g/dL in the darbepoetin alfa group, suggesting slight decreases in Hb levels. However, these changes were within the variation range of 1 g/dL in clinical practice (7). Furthermore, the mean of Hb levels met the targeted Hb levels of ≥10.0 to <12.0 g/dL recommended by the guideline (7) throughout the study: 10.61 ± 0.79 (95% CI, 10.46, 10.76) g/dL in the JR-131 group and 10.56 ± 0.86 (95% CI, 10.40, 10.72) g/dL in the darbepoetin alfa group at the end of treatment. These results suggest that there was no notable change in Hb levels which affected efficacy and safety for patients receiving either JR-131 or darbepoetin alfa. In one subject of the JR-131 group receiving the 120 μg dose in the observation period, the dose increased to 140 μg at Week 21 and they completed the study; on the other hand, another subject in the darbepoetin alfa group receiving 120 μg of darbepoetin alfa from the observation period was discontinued from the study at Week 8 at the discretion of the investigator. As a result, the total administered dose in the darbepoetin alfa group was less than that of JR-131, but there were no statistically significant differences between the groups in the total administered dose and change in the dose during the treatment period. These suggest that the equivalence in efficacy was not due to the administered dose difference.

There was no significant difference in the incidence of TEAEs between JR-131 and darbepoetin alfa groups. The ADRs observed in the JR-131 group in this study were aspartate aminotransferase increased (n = 1) and blood creatine phosphokinase increased (n = 1), and in the darbepoetin alfa group, it was hypertension (n = 1). Onset times of TEAEs were similar between the groups during the treatment

period, and no TEAEs were observed with a high incidence in a specific time period. Common TEAEs with an incidence ≥5% were not considered related to the study drugs, and these were generally observed in patients with CKD and those undergoing hemodialysis, or they occurred incidentally.

A biosimilar of epoetin alfa was first approved in Europe in 2007. Several biosimilars of epoetin alfa are currently used for treating renal anemia in many countries and contributes to cost reduction in the healthcare system (14,15). Epoetin kappa is the only epoetin alfa biosimilar approved in Japan, and its use in dialysis patients with renal anemia has been growing. JR-131, the first domestic-produced biosimilar of darbepoetin alfa in Japan, could reduce the cost of dialysis by more than epoetin kappa, since darbepoetin alfa is the most common ESA (8).

There are, however, some limitations to this study. First, there was a weakness in blinding of the study drugs. The prefilled syringes of JR-131 were not matched to those of darbepoetin alfa, because the darbepoetin alfa preparations were purchased from the market. Therefore, to maintain blinding, the study drug was administrated only by unblinded study staff, and the patients and assessor did not know the allocation. The assessors included anyone determining subject eligibility, evaluating the endpoints, or assessing adherence. Efficacy bias could be ruled out, because the objective Hb level was used as the clinical outcome.

Secondary intravenous iron preparation was administered at the investigator's discretion. It is reported that dialysis patients with TSAT below 20% showed constantly lower Hb levels and a higher ESA resistance index, suggesting renal anemia due to iron deficiency (16). Therefore, a dose adjustment study of ESAs after treatment of iron deficiency renal anemia with an iron preparation should be considered. However, a notable difference between the groups was not found in the use of intravenous iron preparations throughout the study.

CONCLUSION

The results of this study demonstrate that JR-131 was therapeutically equivalent to darbepoetin alfa in the treatment of hemodialysis patients with renal anemia. The safety profile of JR-131 over 24 weeks was similar to that of darbepoetin alfa. No patients developed anti-JR-131/darbepoetin alfa antibodies. As a result, JR-131 is a useful darbepoetin alternate for the management of dialysis patients with renal anemia at a lower cost.

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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 fees from Kyowa Hakko Kirin Pharmaceutical. Kazuhiko Tsuruya, Ikuto Masakane, and Hidetomo Nakamoto report receiving lecture fees and grants from Kyowa Hakko Kirin Pharmaceutical and Chugai Pharmaceutical. Masayuki Yamada is an employee of Kissei Pharmaceutical.

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SUPPORTING INFORMATION

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FIG. S1. Dose distribution (FAS): (A) JR-131 and (B) darbepoetin alfa.

FIG. S2. Percentage of iron preparations use (FAS).