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Randomized, Double-Blinded, Active-Controlled (Darbepoetin Alfa), Phase 3 Study of Vadadustat in Chronic Kidney Disease Patients With Anemia on Hemodialysis in Japan

Masaomi Nangaku[1]
Kazuoki Kondo[2]
Kiichiro Ueta[2]
Yoshimasa Kokado[2]
Genki Kaneko[2]
Hiroki Matsuda[2]
Yutaka Kawaguchi[2]
Yasuhiro Komatsu[3]

[1]The University of Tokyo School of Medicine, Tokyo, Japan

[2]Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

[3]Gunma University, Graduate School of Medicine, Maebashi, Gunma, Japan

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Disclosures

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Potential conflicts of interest

- Masaomi Nangaku has received honoraria, advisory fees, or research funding from Akebia, Alexion, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, GSK, JT, Kyowa Kirin, Mitsubishi Tanabe, Ono, Takeda, and Torii.
- Genki Kaneko, Yutaka Kawaguchi, Yoshimasa Kokado, Kazuoki Kondo, Hiroki Matsuda, and Kiichiro Ueta are employees of Mitsubishi Tanabe Pharma Corporation.
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Introduction

Background

- Vadadustat (VDT) is an investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) under development for the treatment of anemia in patients with CKD
- Phase 2 trials for the treatment of anemia in patients with NDD-CKD and HD-CKD have been conducted[1-4]
- This study in Japan is the first double-blind, active-controlled phase 3 study (NCT03439137) of VDT for treatment of anemia in patients with HD-CKD for up to 52 weeks

Objectives

- The primary endpoint was to demonstrate noninferiority of VDT in average Hb at weeks 20 and 24 compared with DA for treatment of anemia in patients with HD-CKD who were receiving ESAs
- Here, we present the results for the prespecified primary analysis up to week 24 and recently available data for durability of efficacy and long-term safety up to week 52

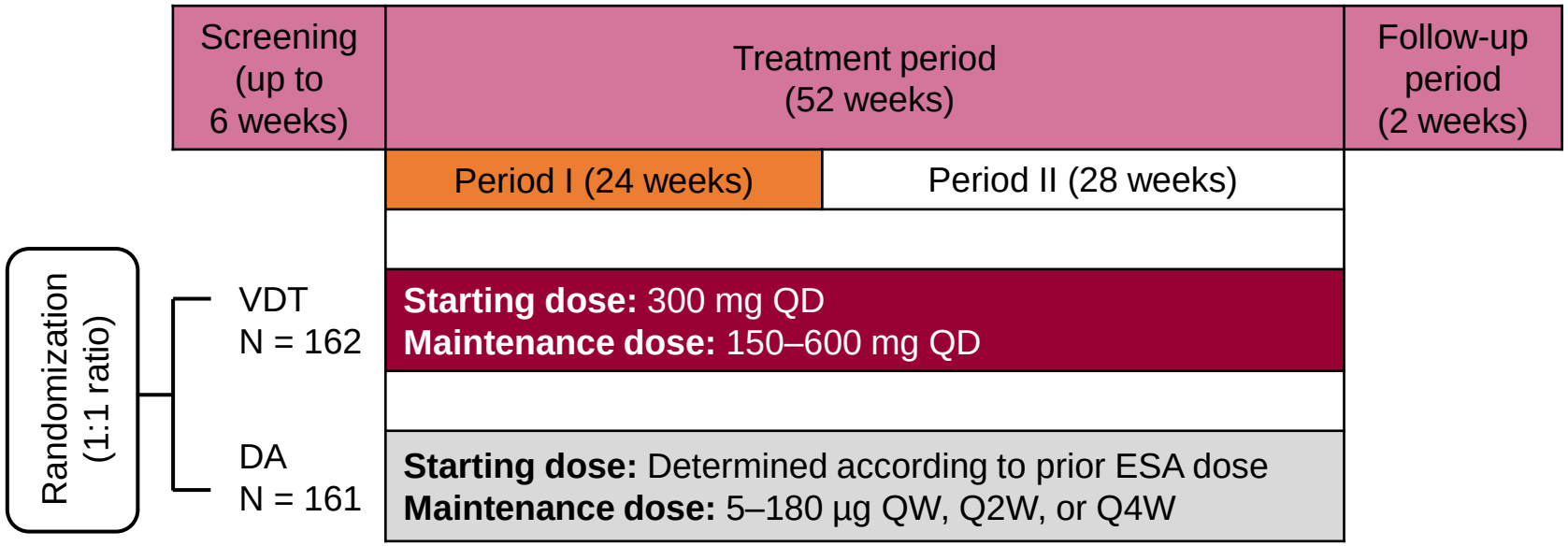
DA, darbepoetin alfa; Hb, hemoglobin; HD, hemodialysis-dependent; NDD, nondialysis-dependent; VDT, vadadustat.

1. Pergola PE, et al. Kidney Int. 2016;90(5):1115–22; 2. Martin ER, et al. Am J Nephrol. 2017;45:380–88; 3. Haase VH, et al. Nephrol Dial Transplant. 2019;34(1):90–99;
4. Nangaku M, et al. ASN Kidney Week, San Diego, CA, USA; October 23–28, 2018.

Study Design

Multicenter, randomized, double-blinded, active-controlled, double-dummy, phase 3, conducted in Japan

- **Target Hb:** 10.0–12.0 g/dL
- **Main dose adjustment algorithm:** adjusted VDT and DA to maintain target Hb
  - Dose increase: Hb <10.0 g/dL; dose reduction: Hb >11.5 g/dL
  - Interval for dose increase: ≥4 weeks for VDT and ≥2 weeks for DA
- **Iron supplementation:** administered to maintain serum ferritin ≥100 ng/mL or TSAT ≥20%



Q2W, once every 2 weeks; Q4W, once every 4 weeks; QD, once daily; QW, once every week; TSAT, transferrin saturation.

Key Inclusion Criteria

- **Age:** ≥20 years
- **Hemodialysis status:** hemodialysis or hemodiafiltration 3 times/week for ≥12 weeks before screening
- **ESA use:** had used same ESA for ≥8 weeks before screening
  - Epoetin alfa, epoetin beta, or epoetin kappa (≤9000 IU/week)
  - Darbepoetin alfa (≤60 µg/week)
  - Epoetin beta pegol (≤250 µg/4 weeks)
- **Baseline Hb level:** ≥9.5 to ≤12.0 g/dL
- **Iron parameters:** serum ferritin ≥100 ng/mL or TSAT ≥20%

Statistical Analysis

Primary Endpoint (FAS)

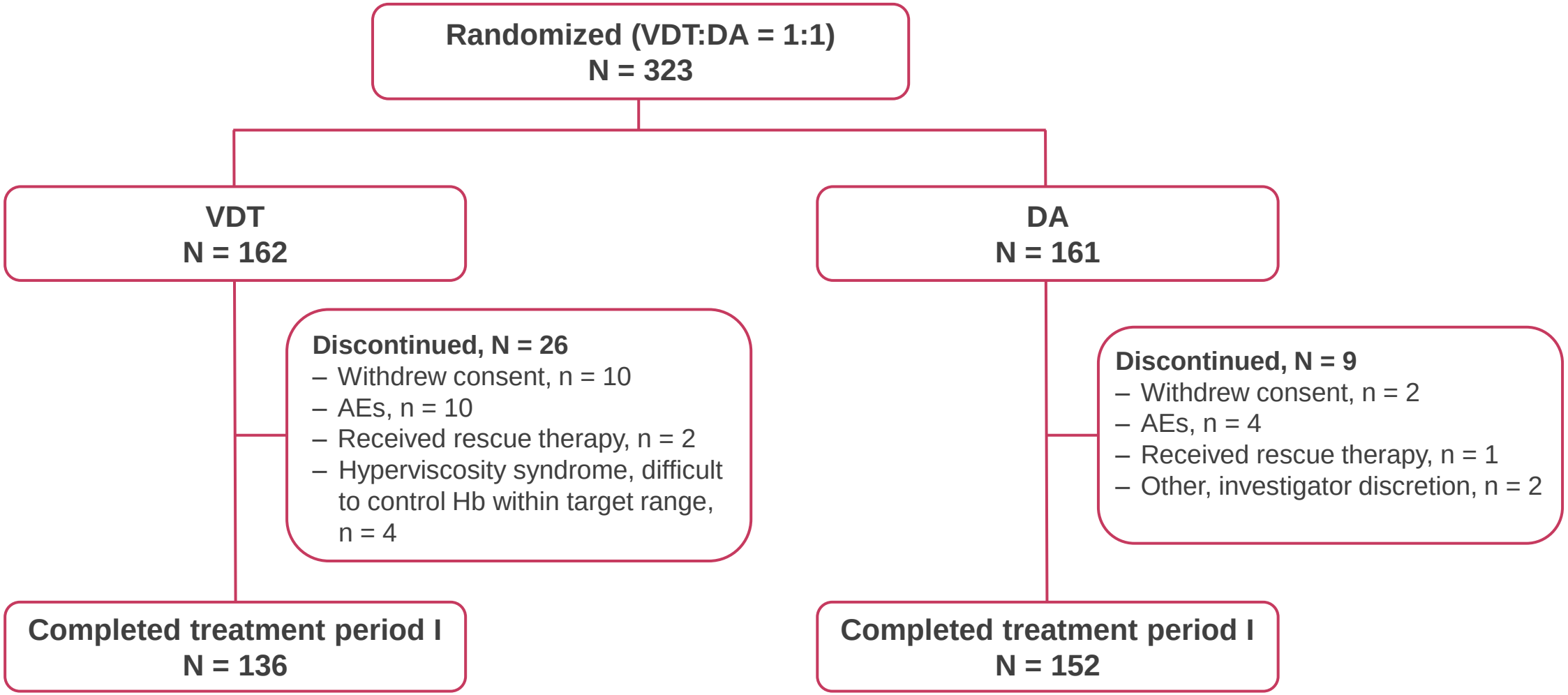
- Noninferiority: VDT was considered noninferior to DA if the 95% CI lower limit for the difference between VDT and DA in the LSMean of the average Hb at weeks 20 and 24 was more than or equal to the predefined noninferiority margin of –0.75 g/dL
  - Difference in LSMean: MMRM with an unstructured covariance matrix within patients

Sample Size

- Planned sample size: 300 enrolled and randomized patients (VDT: 150 patients; DA: 150 patients)
- This sample size was calculated to give 95% power for noninferioity with a two-sided alpha of 0.05 based on the following assumptions: the average Hb at weeks 20 and 24 for DA = 11.0 g/dL, difference in average Hb between VDT and DA = 0, with a noninferiority margin of –0.75 g/dL and standard deviation of 1.73 g/dL

CI, confidence interval; FAS, full analysis set; LS, Least Squares; MMRM, mixed-model repeated measures.
FAS: patients with ≥1 study drug dose and ≥1 efficacy measurement after randomization; SAF: safety analysis set; all patients with ≥1 dose of study drug.

Patient Disposition



AE, adverse event.

Patient Characteristics at Baseline (FAS)

Characteristic	VDT N = 162		DA N = 161	
Sex (male), n (%)	104 (64.2)		109 (67.7)	
Age (years)	66.0 ± 11.3		64.9 ± 11.7	
Body weight (kg) (dry weight)	58.1 ± 11.9		58.8 ± 13.8	
BMI (kg/m^2)	22.4 ± 3.4		22.4 ± 4.5	
Hb (g/dL)	10.73 ± 0.7		10.73 ± 0.7	
Duration of dialysis (years)	7.4 ± 6.7		7.6 ± 7.6	
Serum ferritin (ng/mL)	144.5 ± 139.6		140.0 ± 95.3	
TSAT (%)	28.6 ± 10.6		26.9 ± 9.4	
Prior ESA	**n (%)**	**Weekly dose**	**n (%)**	**Weekly dose**
Epoetin (IU)	49 (30.2)	3704 ± 2118	53 (32.9)	4783 ± 3183
Darbepoetin alfa (µg)	97 (59.9)	17.2 ± 12.2	90 (55.9)	18.7 ± 14.1
Epoetin beta pegol (µg)	16 (9.9)	18.8 ± 12.1	18 (11.2)	22.9 ± 17.4
Comorbidities, n (%)				
Hypertension	152 (93.8)		147 (91.3)	
Diabetes mellitus	35 (21.6)		49 (30.4)	
Dyslipidemia	59 (36.4)		79 (49.1)	

Data are mean ± SD unless otherwise noted.

Primary Endpoint (FAS)

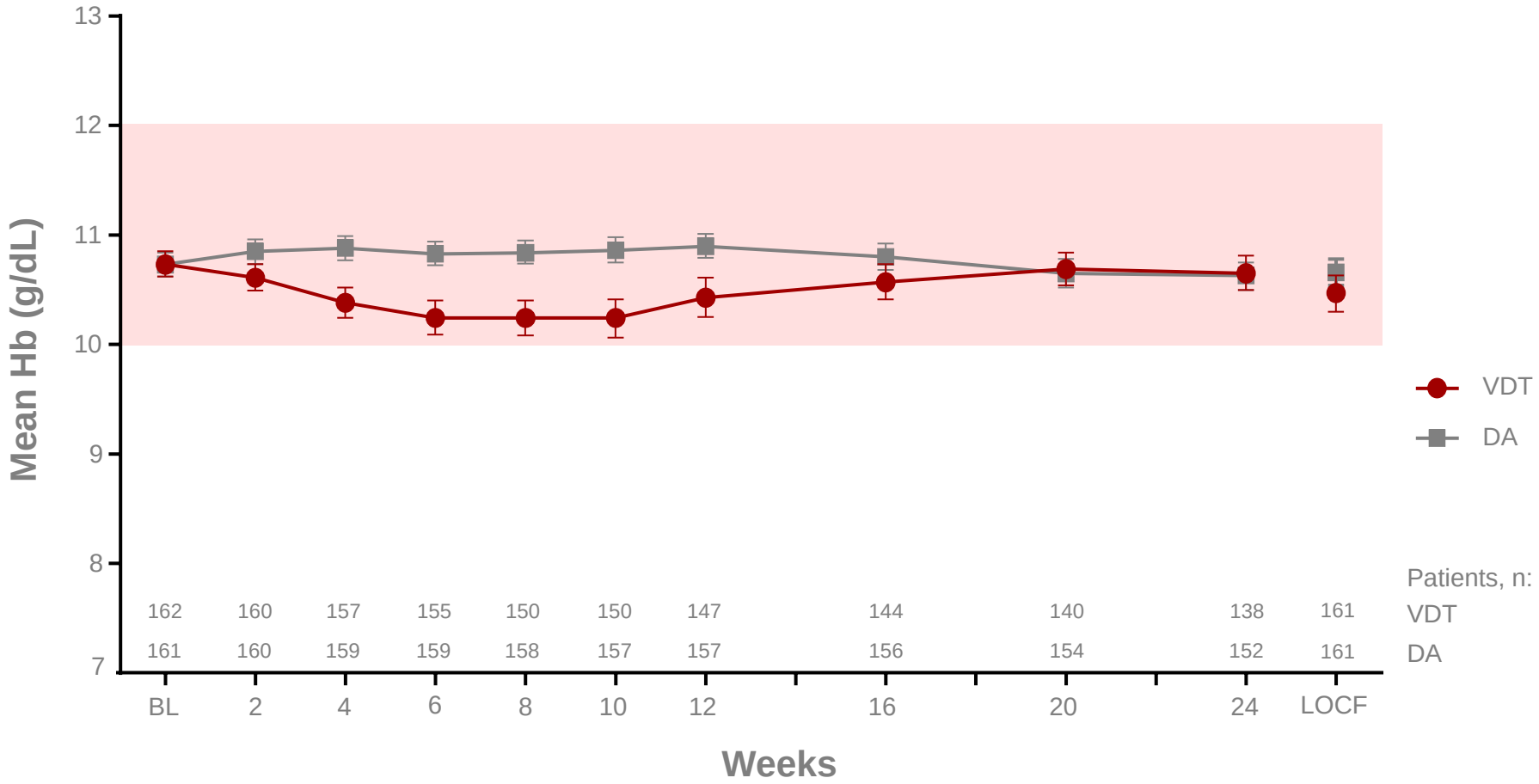
- VDT demonstrated noninferiority to DA as measured by average Hb at weeks 20 and 24
  - The 95% CIs for both the VDT and DA groups were within the target Hb range of 10.0–12.0 g/dL
  - The 95% CI lower limit of the difference between groups (VDT–DA) was above the predefined noninferiority margin of –0.75 g/dL, confirming the noninferiority of VDT to DA

LSMean of the average Hb at weeks 20 and 24 and the difference between VDT and DA

		Average Hb, weeks 20 and 24	
Treatment group	**N**	**LSMean***	**95% CI**
VDT	160	10.61	10.45, 10.76
DA	160	10.65	10.50, 10.80
Difference (VDT–DA)		–0.05	–0.26, 0.17

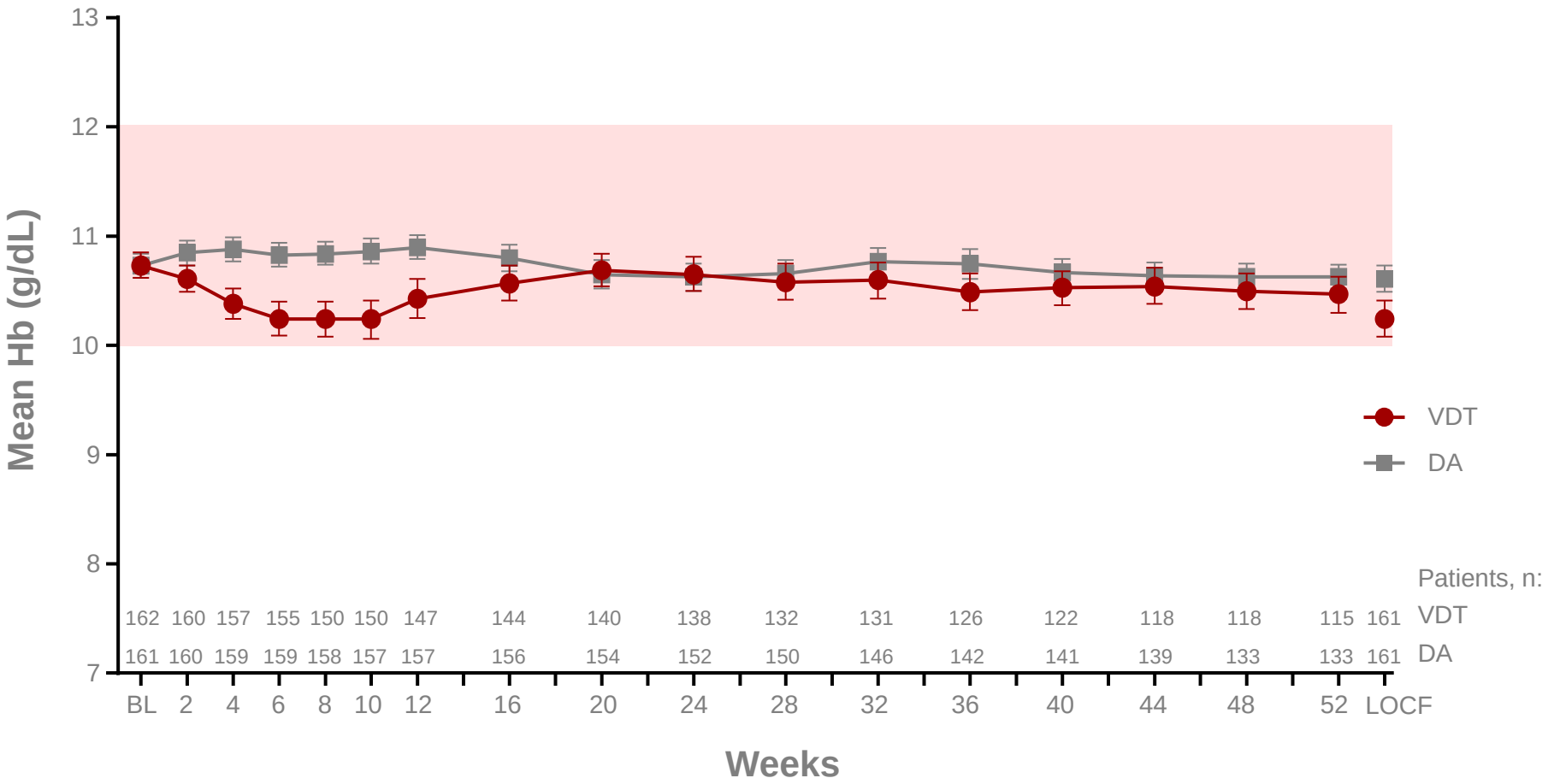
*This MMRM model included treatment group, visits, interaction of treatment group and visits as fixed effects, baseline values as covariate effects, and subject as a random effect (covariance matrix: unstructured).

Mean Hb Over Time, 24 Weeks (FAS)



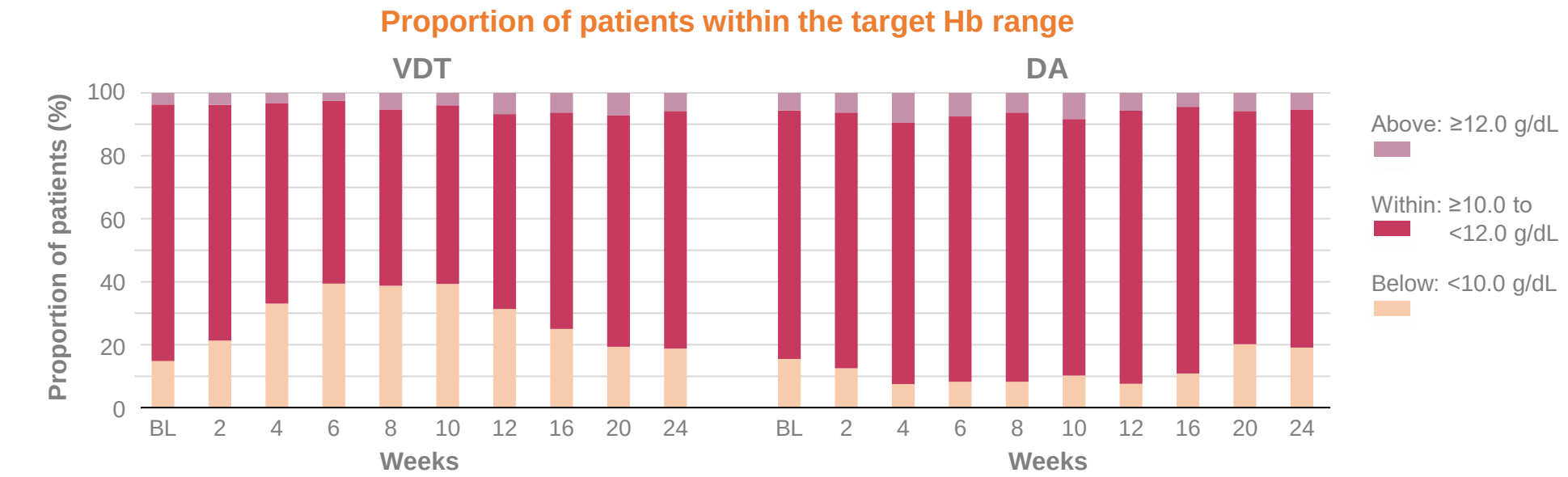
Data are mean (95% CI).
BL, baseline; LOCF, last observation carried forward.

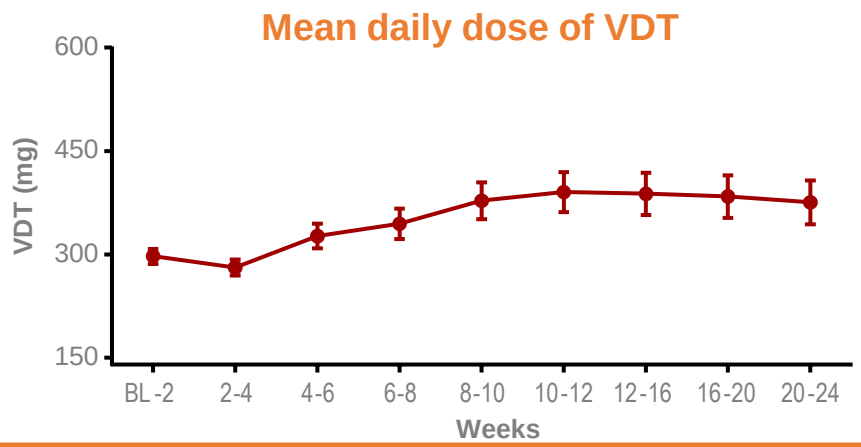
Mean Hb Over Time, 52 Weeks (FAS)

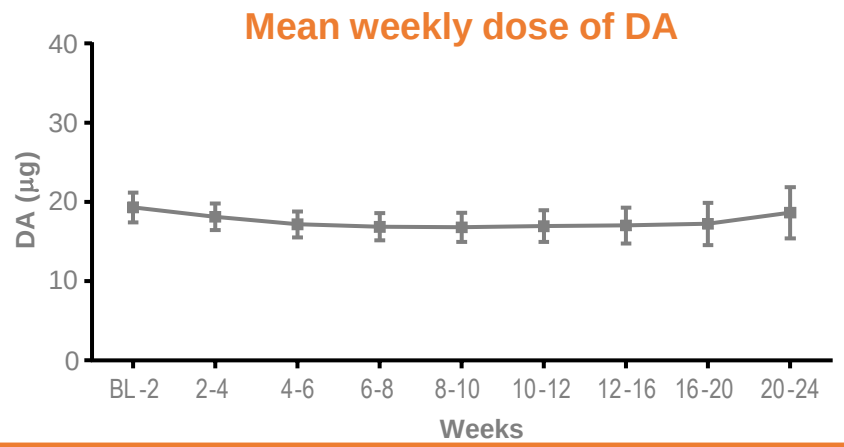


Data are mean (95% CI).
BL, baseline; LOCF, last observation carried forward.

Maintenance Rate of Target Hb Level (FAS)



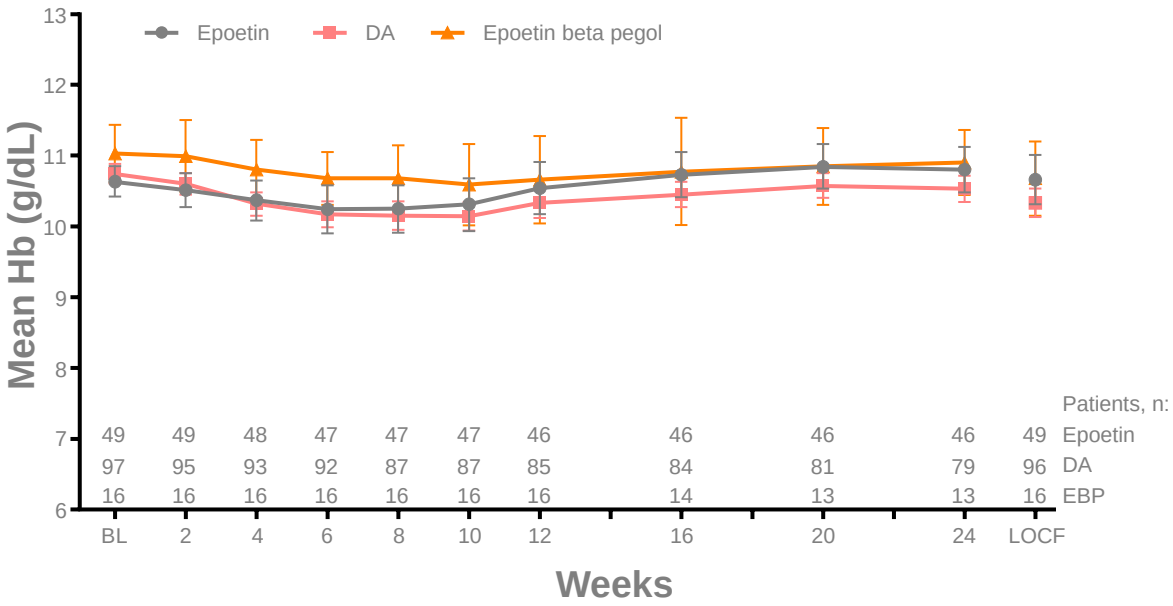




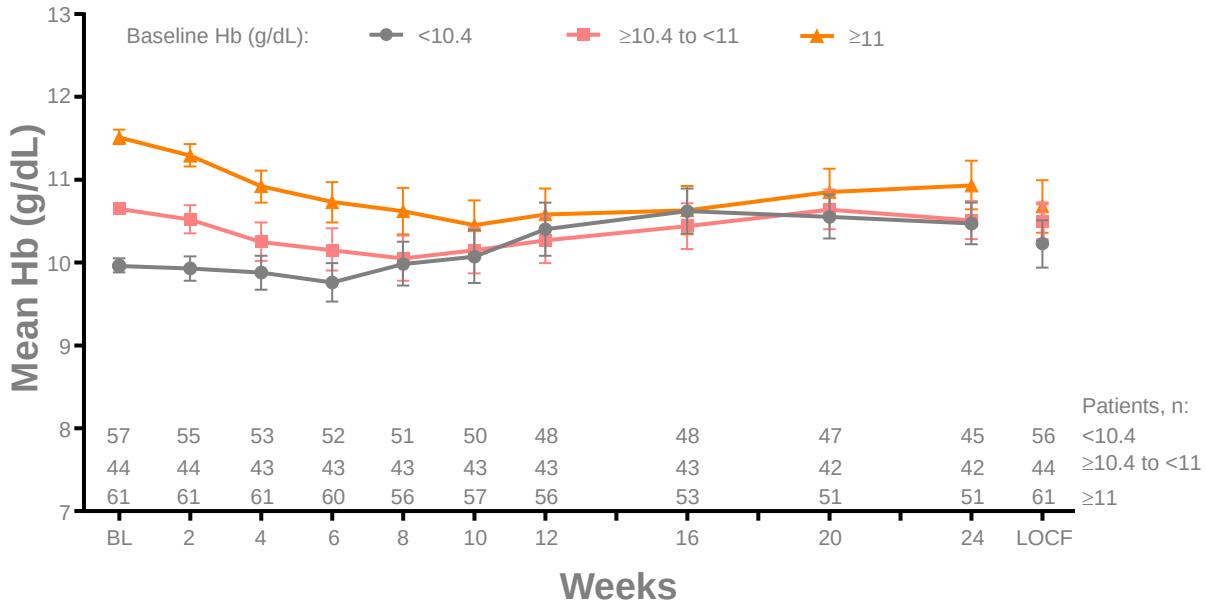
Data for average dose are mean (95% CI).
BL, baseline.

Mean Hb Over 24 Weeks in VDT-Treated Subgroups Stratified by Prior ESA or Baseline Hb (FAS)

Mean Hb by prior ESA therapy

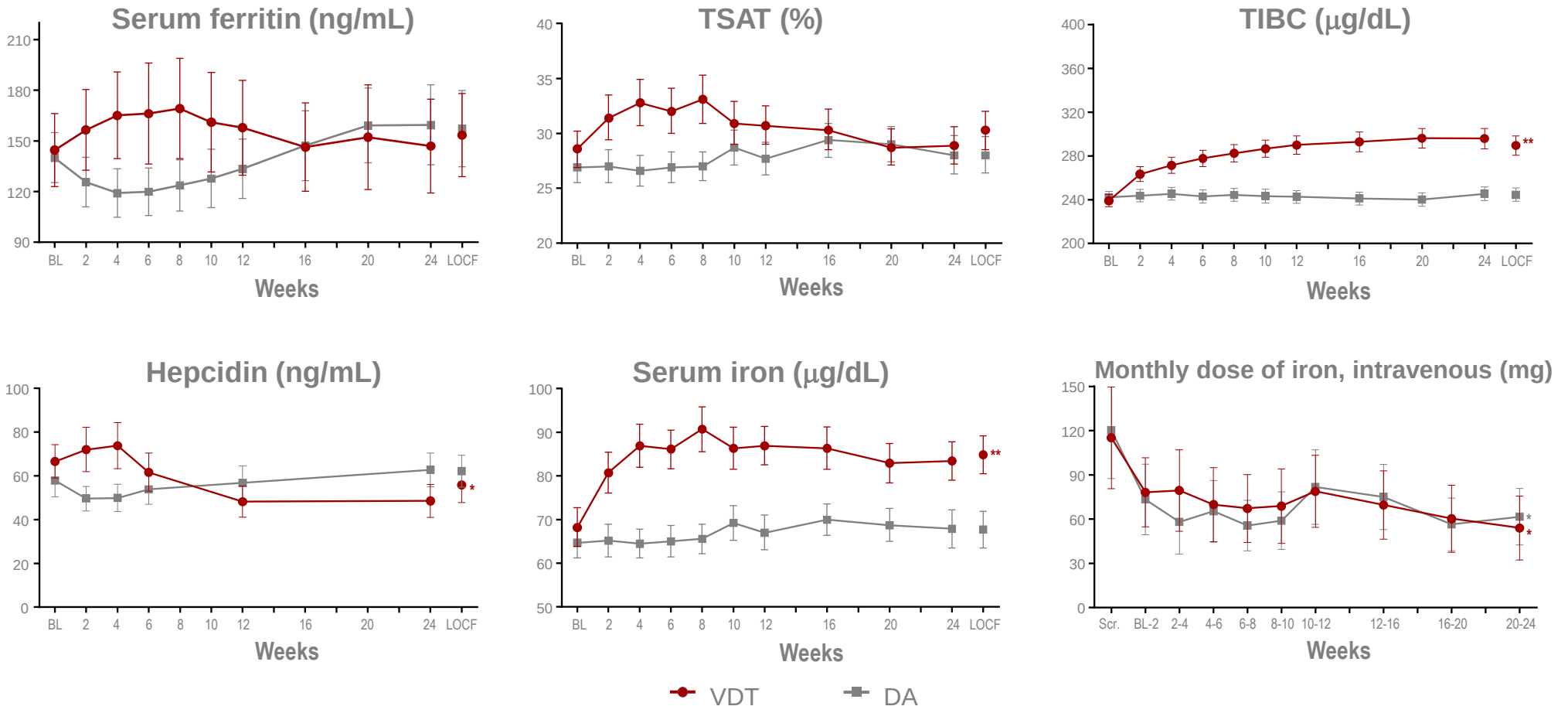


Mean Hb by baseline Hb



Data are mean (95% CI).
BL, baseline; LOCF, last observation carried forward.

Iron-Related Parameters (FAS)



All data are mean (95% CI).
Paired *t*-test compared with BL for all parameters except monthly dose of iron, which is compared with the screening period: *p<0.01; **p<0.001.
BL, baseline; LOCF, last observation carried forward; Scr., screening; TIBC, total iron-binding capacity.

Safety Results, 52 Weeks (SAF)

Overview, n (%)	VDT (N = 162)	DA (N = 161)
Subjects with ≥1 AE	154 (95.1)	158 (98.1)
Adverse drug reaction	18 (11.1)	6 (3.7)
Serious AEs	41 (25.3)	44 (27.3)
Serious adverse drug reaction	0 (0.0)	0 (0.0)
Discontinuation due to AEs	16 (9.9)	14 (8.7)
Dose reduction or interruption of study drug due to AEs	13 (8.0)	4 (2.5)
Deaths due to AEs	2 (1.2)	1 (0.6)
Most common AEs with VDT, n (%)	**VDT (N = 162)**	**DA (N = 161)**
Nasopharyngitis	74 (45.7)	73 (45.3)
Diarrhea	25 (15.4)	24 (14.9)
Shunt stenosis	23 (14.2)	26 (16.1)
AEs of special interest, n (%)	**VDT (N = 162)**	**DA (N = 161)**
Cardiovascular event, cardiac failure	13 (8.0)	15 (9.3)
Retinal disorder	21 (13.0)	16 (9.9)
Malignancy	7 (4.3)	9 (5.6)
Hyperkalemia	1 (0.6)	1 (0.6)
Pulmonary hypertension	0 (0.0)	0 (0.0)

AE, adverse event.

Conclusions

- This study demonstrated noninferiority of VDT to DA
- Mean Hb levels in the VDT group were maintained within the target range throughout the 52-week treatment period. Durability of efficacy was confirmed up to week 52
- VDT significantly decreased hepcidin from baseline to week 24, suggesting an improvement in iron metabolism
- Overall, no new safety concerns were identified
- In this study, no meaningful imbalance between groups was observed in the proportion of patients who reported AEs of special interest; however, the AEs of special interest (cardiovascular event, cardiac failure, retinal disorder, malignancy, hyperkalemia, pulmonary hypertension) need to be further investigated across the HIF-PHI class
- These findings support the usefulness of VDT for treating anemia in Japanese patients with CKD on hemodialysis who convert from ESA therapy