

Efficacy and Safety of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, Being Evaluated for the Treatment of Anemia Due to Chronic Kidney Disease (CKD) in Japanese Subjects: Results from Phase 2 Studies

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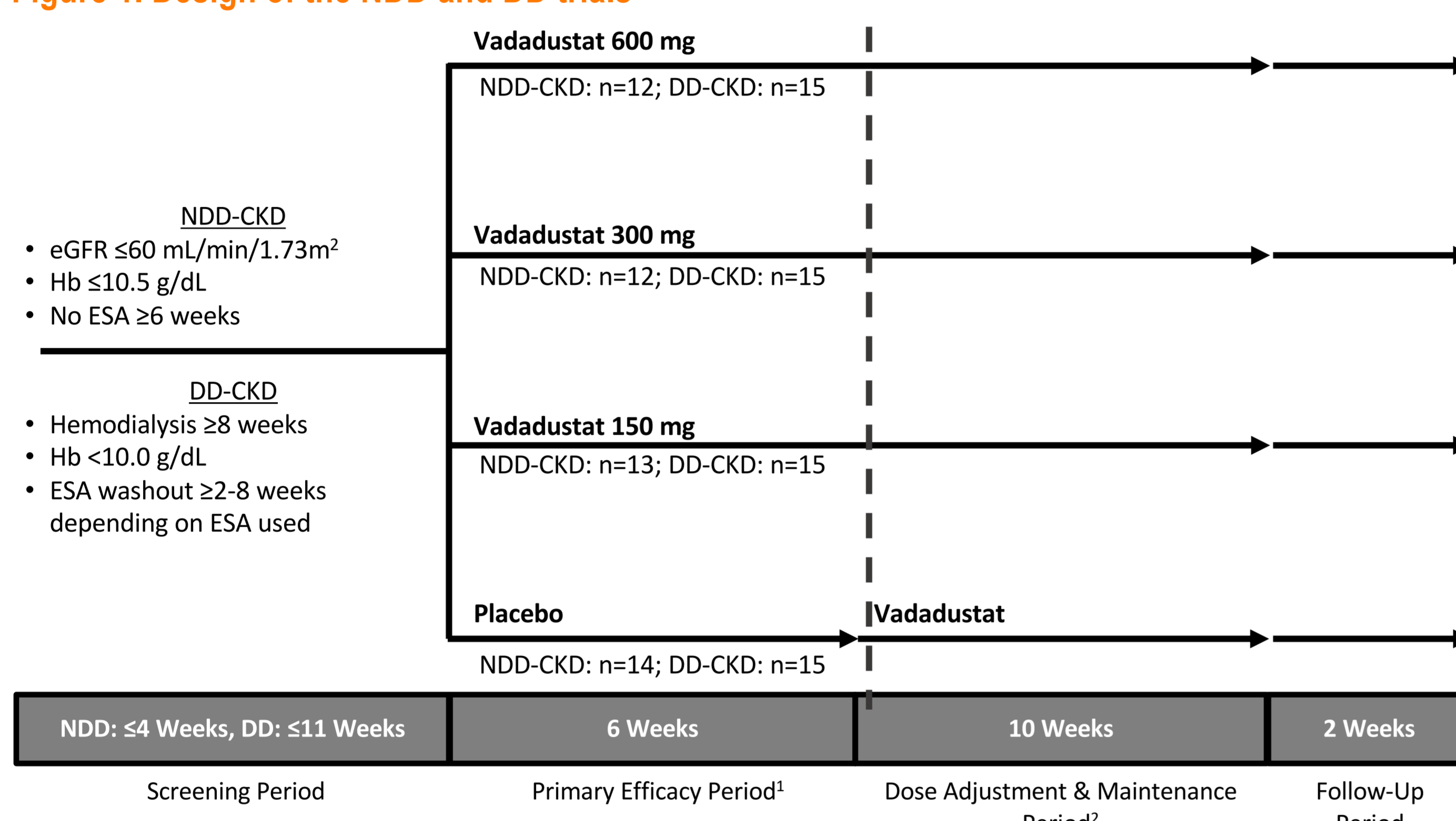
BACKGROUND

- Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia associated with non-dialysis-dependent (NDD) and dialysis-dependent (DD) chronic kidney disease (CKD)
- In prior phase 2 studies, vadadustat increased hemoglobin (Hb) levels and improved biomarkers associated with iron utilization and mobilization in anemic CKD patients (Pergola et al., *Kidney Int*, 2016; Martin et al., *AJN*, 2017; Haase et al., *NDT*, 2018)
- Vadadustat was investigated in two phase 2, randomized, double-blind, placebo-controlled trials in Japanese CKD subjects with anemia due to NDD (CI-0021, NCT03054337) and DD (CI-0022, NCT03054350)
- The primary objective of these studies was to assess the dose-response relationship based on the change in Hb concentration following daily oral administration of vadadustat for 6 weeks

METHODS

- The two trials included a 6-week fixed-dose, double-blind, placebo-controlled, primary efficacy period and a 10-week active treatment, dose adjustment and maintenance period
- At the primary efficacy period, subjects were randomized 1:1:1:1 to vadadustat 150 mg, 300 mg, 600 mg, or placebo (Figure 1)
- At the start of the dose adjustment and maintenance period, subjects randomized to placebo were switched to vadadustat 150 mg, 300 mg, or 600 mg (Figure 1). For all subjects, vadadustat dose was adjusted to achieve target Hb range (10-12 g/dL) during this period.
- Statistical analysis: For the primary efficacy analysis in each study, an analysis of covariance (ANCOVA) model was used in the modified intention-to-treat (mITT) population (Figure 2) to compare mean change in Hb from baseline (pretreatment average) to Week 6 between the vadadustat and placebo groups
 - mITT population included all randomized subjects receiving at least one dose of study medication and had pre-treatment Hb average and at least one post-baseline Hb measurement. Safety population included all enrolled subjects receiving at least one dose of study medication
 - Missing values were imputed using last observation carried forward (LOCF)

Figure 1. Design of the NDD and DD trials



eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.
¹Dose increases not permitted; dose decrease as needed per protocol-specified guidelines for rapid Hb rise or Hb>13 g/dL.
²Dose adjusted per protocol-specified guidelines to achieve target Hb 10-12 g/dL. Subjects randomized to placebo were switched to vadadustat at the beginning of the dose adjustment and maintenance period.

RESULTS

Table 1. Baseline characteristics of NDD and DD subjects: mITT population

	NDD Study		DD Study		
	Vadadustat	Placebo	Vadadustat	Placebo	
mITT population, n	37	14	44	14	
Age, years	69.8 (11.7)	71.4 (11.6)	63.3 (9.2)	65.7 (11.6)	
Female, n (%)	18 (49)	4 (29)	12 (27)	6 (43)	
Weight, kg	59.2 (12.4)	58.0 (10.3)	60.7 (14.8)	52.6 (11.0)	
BMI, kg/m ²	24.3 (4.5)	22.4 (3.4)	24.0 (4.5)	22.4 (4.0)	
Diabetes mellitus*, n (%)	12 (32)	8 (57)	22 (50)	6 (43)	
Etiology of CKD*, n (%)					
Hypertension	15 (41)	8 (57)	13 (30)	6 (43)	
Diabetes	6 (16)	6 (43)	19 (43)	5 (36)	
Autoimmune/GN/Vasculitis	8 (22)	2 (14)	13 (30)	5 (36)	
Pre-treatment Hb, g/dL	9.7 (0.7)	9.9 (0.6)	9.0 (0.6)	8.97 (0.6)	
eGFR, mL/min/1.73m ²	17.8 (10.3)	22.0 (9.8)	NA	NA	
CKD status	CKD Stage, n (%)		Vintage dialysis, years		
	G3a	1 (3)	0	6.1 (6.5)	7.6 (9.9)
	G3b	6 (16)	2 (14)		
	G4	10 (27)	8 (57)		
	G5	20 (54)	4 (29)		

BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin.
*Multiple etiologies were allowed in this field. Only the 3 most frequent are listed.
Data are presented as n (%) or mean (SD).
G3a, eGFR 45-59 mL/min/1.73m²; G3b, eGFR 30-44 mL/min/1.73m²; G4, eGFR 15-29 mL/min/1.73m²; G5, eGFR <15 mL/min/1.73m².

Efficacy

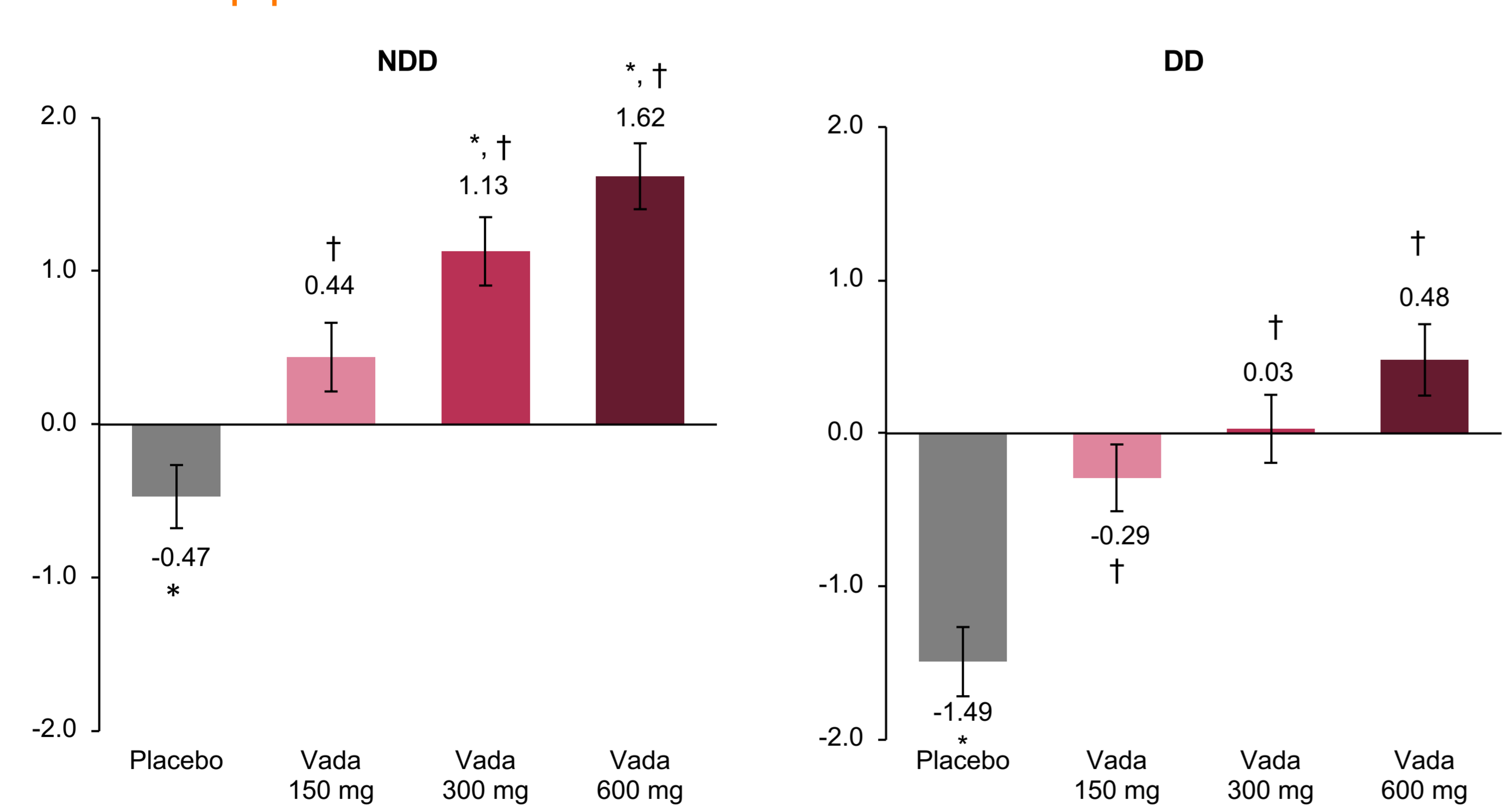
NDD study: mITT population (N=51)

- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed for each vadadustat treatment group vs placebo at the end of the primary efficacy period (Week 6) (Figure 2 and Figure 3)
- All NDD subjects who received vadadustat achieved or exceeded target Hb levels at some point during the trial
 - All subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period) exhibited Hb levels of ≥10 g/dL. 90.9% exhibited Hb levels within the target range of 10 to 12 g/dL at the end of treatment visit and 9.1% exhibited Hb levels above the target range
- No subjects required ESA or RBC transfusion rescue during the primary efficacy period. During the dose adjustment and maintenance period, 1 subject each in the 300 mg vadadustat, 600 mg vadadustat, and placebo converting to vadadustat groups required RBC transfusion rescue; 2 subjects in the 300 mg group and 1 in the 600 mg group required ESA rescue

DD study: mITT population (N=58)

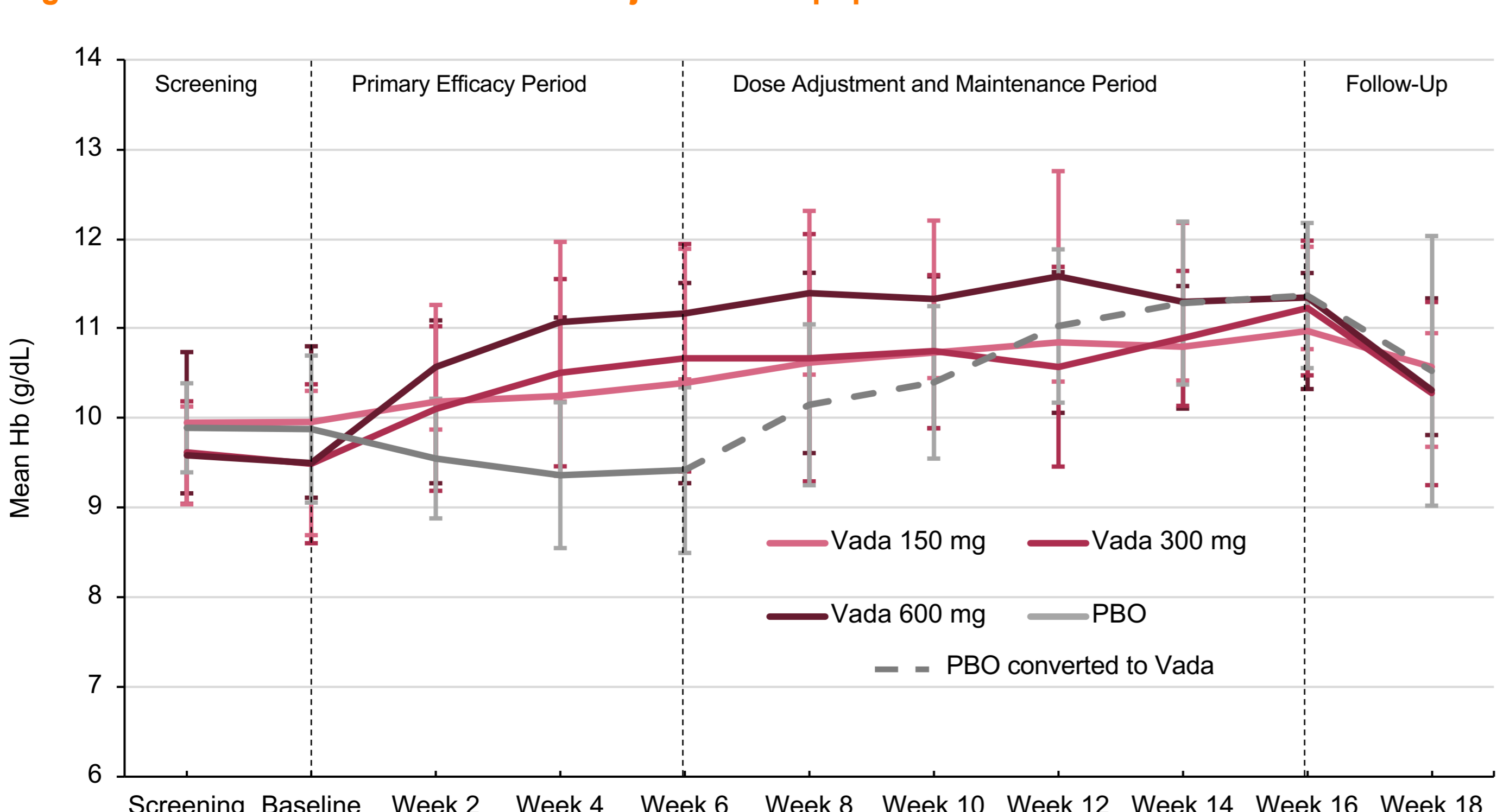
- Statistically significant dose-dependent increases from baseline in mean Hb levels were observed for each vadadustat treatment group vs placebo at the end of the primary efficacy period (Week 6) (Figure 2 and Figure 4)
- Among subjects initially randomized to vadadustat who completed 16 weeks of treatment (primary efficacy period and dose adjustment and maintenance period), 71.4% exhibited Hb levels within the target range of 10 to 12 g/dL at the end of treatment visit, 8.6% exhibited Hb levels above the target range, and 20.0% exhibited Hb levels below the target range
- During the primary efficacy period, 3 (21%) subjects in the placebo group and 1 (8%) in the 600 mg group required RBC transfusion rescue, and 8 (57%) in the placebo group, and 4 (27%), 2 (13%), and 1 (7%) in the 150, 300, and 600 mg groups, respectively, required ESA. During the dose adjustment and maintenance period, 1 (7%) in the 150 mg group required RBC transfusion, and 1 (7%) in the placebo group and 1 (7%) in the 600 mg group required ESA rescue

Figure 2. Observed mean change in Hb (g/dL) between baseline (pretreatment average) and Week 6: mITT population



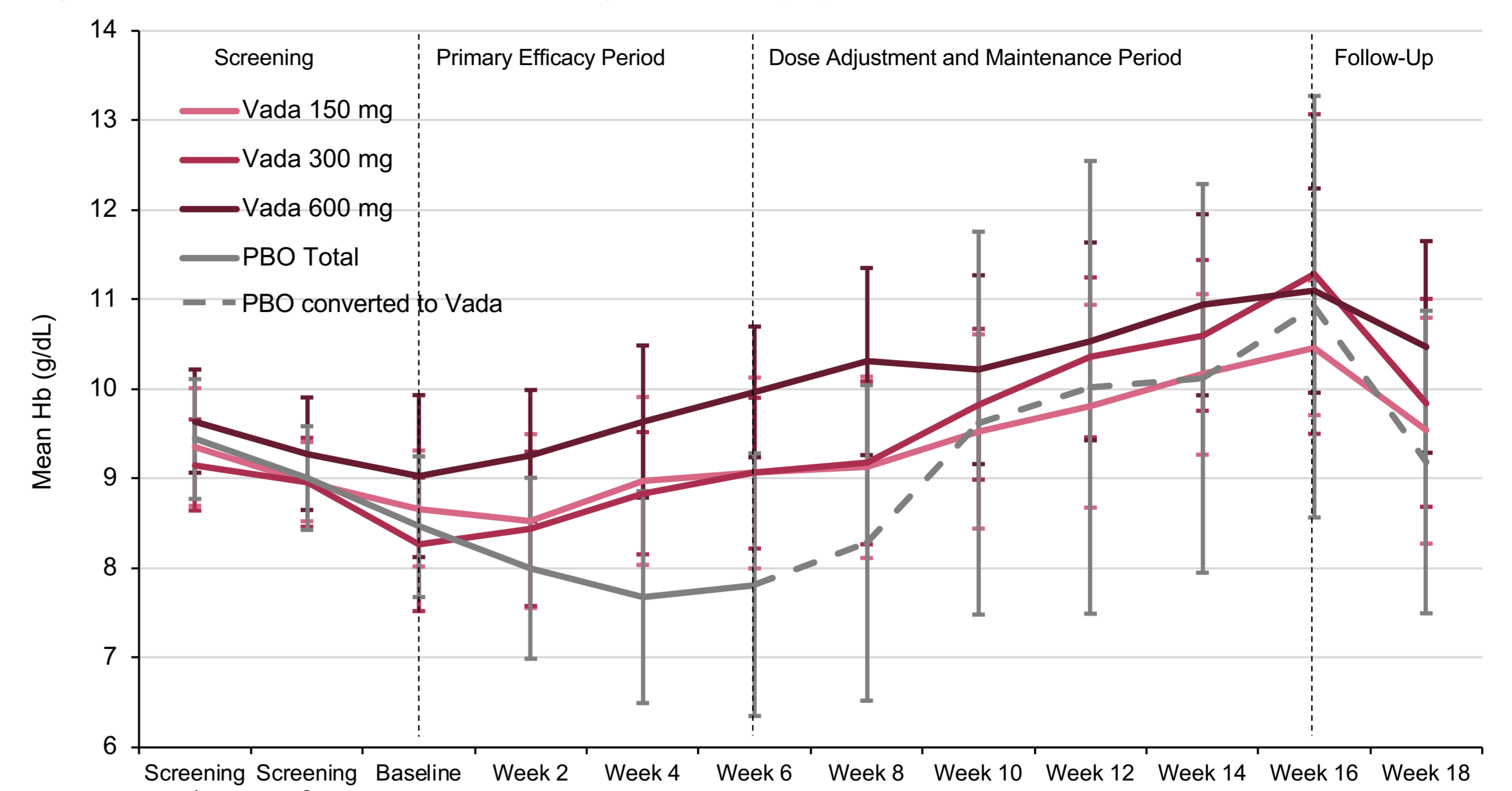
Vada, vadadustat.
Statistical methodology: ANCOVA [P<0.0001]; mITT LOCF. *P<0.05 vs baseline. †P<0.05 vs placebo. Error bars represent standard error.

Figure 3. Mean Hb over time in NDD subjects: mITT population



Vada, vadadustat, PBO, placebo.
Error bars represent standard deviation.

Figure 4. Mean Hb over time in DD subjects: mITT population



Vada, vadadustat, PBO, placebo.
Error bars represent standard deviation.

NDD and DD iron-related parameters: mITT Population

- Statistically significant, dose-dependent decreases in ferritin and hepcidin and increases in total iron binding capacity (TIBC) were observed with vadadustat administration from baseline to Week 6 (Table 2)
- In the NDD study, all vadadustat dosages resulted in a statistically significant decrease from baseline in transferrin saturation (TSAT) at Week 6 but not compared with placebo. In the DD study, vadadustat at 300 and 600 mg resulted in a statistically significant decrease in TSAT from baseline, but only the 600 mg dosage was significantly different from placebo (Table 2)

Table 2. Mean absolute changes in iron indices from baseline to Week 6 in NDD and DD subjects: mITT population

Iron Index	NDD Study				DD Study			
	Placebo* (n=14)	Vadadustat 150 mg (n=12)	Vadadustat 300 mg (n=12)	Vadadustat 600 mg (n=13)	Placebo* (n=6)	Vadadustat 150 mg (n=11)	Vadadustat 300 mg (n=13)	Vadadustat 600 mg (n=13)
TIBC, µg/dL	7.6 (23.55)	44.9† (32.99)	75.2† (35.2)	93.8† (44.74)	15.8† (8.08)	35.4† (28.72)	67.5† (25.72)	80.7† (39.04)
TSAT, %	-4.72 (8.93)	-4.96‡ (7.34)	-7.31† (8.38)	-6.78‡ (10.61)	-2.78 (12.82)	-6.51 (11.62)	-10.14‡ (11.29)	-12.46†† (9.54)
Ferritin, ng/mL	-11.44 (31.41)	-38.48‡ (34.23)	-69.36†† (49.97)	-101.54†† (57.70)	12.63 (32.42)	-51.20†† (58.86)	-68.67†† (54.71)	-104.49†† (49.56)
Hepcidin, ng/mL	-3.82 (18.50)	-24.62† (20.02)	-40.82†† (27.25)	-37.96†† (21.08)	-11.80 (13.65)	-53.47†† (43.55)	-73.59†† (32.35)	-104.30†† (36.76)

n reflects the subset of patients for whom iron indices were collected.
*Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period.
†P<0.05 vs baseline; ††P<0.05 vs placebo.

Safety

- During the primary efficacy period of both studies, adverse events (AEs) were reported at a higher rate in the vadadustat 300 and 600 mg groups than in the 150 mg or placebo groups
- In both studies, most AEs were mild or moderate and assessed by investigator as unrelated to study drug

NDD study: safety population (N=51)

- No serious AEs (SAEs) were reported during the primary efficacy period. During the dose adjustment and maintenance period, 11 subjects reported a total of 13 SAEs. Only one reported SAE was determined to be drug-related (abnormal hepatic function). No deaths were reported
- Treatment-emergent AEs (TEAEs) occurring in >2 of the 37 vadadustat-treated subjects during the primary efficacy period were hypertension (13.5%) and nausea (8.1%). No placebo-treated subjects experienced either of these, and no AE was reported by more than one placebo-treated subject
- TEAEs occurring in >2 of the 51 vadadustat-treated subjects during the dose adjustment and maintenance period included viral upper respiratory tract infection (7.8%), arteriovenous shunt operation (5.9%), constipation (5.9%), and diarrhea (5.9%)
- Three subjects (25%) in the 300 mg and 9 subjects (69.2%) in the 600 mg group had a dose decrease or interruption during the primary efficacy period according to a protocol-defined dose adjustment algorithm

DD study: safety population (N=60)

- Five SAEs were reported in 3 vadadustat-treated subjects. During the dose adjustment and maintenance period, 3 subjects reported a total of 4 SAEs. None of these were determined to be drug-related. No deaths were reported
- TEAEs occurring in >2 of the 45 vadadustat-treated subjects during the primary efficacy period included nasopharyngitis (15.6%), diarrhea (8.9%), and shunt stenosis (6.7%). No TEAE was reported by more than one placebo-treated subject during this period
- TEAEs occurring in >2 of the 45 vadadustat-treated subjects during the dose adjustment and maintenance period included nasopharyngitis (13.3%) and headache (6.7%). No TEAE was reported by >2 placebo-to-vadadustat subjects after they were switched to vadadustat
- One subject (6.7%) in the 150 mg and 3 subjects (21.4%) in the 600 mg group had a dose decrease or interruption during the primary efficacy period according to a protocol-defined dose adjustment algorithm

Table 3. Overview of TEAEs by randomized dose: safety population

TEAE n (%)	NDD Study				DD Study			
	Placebo*	Vadadustat 150 mg	Vadadustat 300 mg	Vadadustat 600 mg	Placebo	Vadadustat 150 mg	Vadadustat 300 mg	Vadadustat 600 mg
Primary Efficacy Period								
	N=14	N=12	N=12	N=13	N=15	N=15	N=15	N=15
Any TEAE	5 (35.7)	4 (33.3)	7 (58.3)	7 (53.8)	6 (40)	8 (53.3)	11 (73.3)	6 (40)
- Mild	4 (28.6)	4 (33.3)	6 (50.0)	7 (53.8)	6 (40)	7 (46.7)	11 (73.3)	5 (33.3)
- Moderate	1 (7.1)	-	1 (8.3)	-	1 (6.7)	1 (6.7)	-	2 (13.3)
- Severe	-	-	-	-	-	-	-	1 (6.7)
Any drug-related TEAE	-	1 (8.3)	3 (25.0)	3 (23.1)	-	-	3 (20.0)	1 (6.7)
TEAE leading to withdrawal	-	-	-	-	-	-	-	1 (6.7)
Serious adverse event	-	-	-	-	1 (6.7)	-	-	3 (20)
Death	-	-	-	-	-	-	-	-
Dose Adjustment and Maintenance Period								
	N=14	N=12	N=12	N=13	N=15	N=15	N=15	N=15
Any TEAE	9 (64.3)	9 (75.0)	10 (83.3)	6 (46.2)	4 (26.7)	9 (60)	9 (60)	9 (60)
- Mild	9 (42.9)	7 (58.3)	10 (83.3)	5 (38.5)	4 (26.7)	9 (60)	9 (60)	9 (60)
- Moderate	3 (21.4)	5 (41.7)	3 (25.0)	2 (15.4)	1 (6.7)	-	2 (13.3)	-
- Severe	1 (7.1)	-	2 (16.7)	1 (7.7)	-	1 (6.7)	-	-
Any drug-related TEAE	1 (7.1)	2 (16.7)	1 (8.3)	-	2 (13.3)	-	-	-
TEAE leading to withdrawal	1 (7.1)	-	2 (16.7)	1 (7.7)	-	1 (6.7)	-	1 (6.7)
Serious adverse event	4 (28.6)	-	5 (41.7)	2 (15.4)	-	1 (6.7)	1 (6.7)	1 (6.7)
Death	-	-	-	-	-	-	-	-

*Placebo group switched to vadadustat at the beginning of the dose adjustment and maintenance period

NDD study Hb excursions: mITT population

- No vadadustat-treated subject had Hb levels >13 g/dL during the primary efficacy period. Three subjects in the dose adjustment and maintenance period each had 1 occurrence of Hb levels >13 g/dL. Hb levels fell below 13 g/dL for all 3 of these subjects within 2 weeks after protocol-specified interruption of treatment with vadadustat
- During the 6-week primary efficacy period, Hb values in the >12 to 13 g/dL range were reported for 8 (21.6%) subjects randomized to receive vadadustat
- During the dose adjustment and maintenance period, Hb values in the >12 to 13 g/dL range occurred in 13 (35.1%) subjects in the vadadustat group, and 5 (35.7%) in the placebo group that switched to vadadustat

DD study Hb excursions: mITT population

- No vadadustat-treated subject had Hb levels >13 g/dL during the primary efficacy period. Two subjects in the dose adjustment and maintenance period each had 1 occurrence of Hb levels >13 g/dL. Hb levels fell below 13 g/dL for both of these subjects within 2 weeks after protocol-specified interruption of treatment with vadadustat
- During the 6-week primary efficacy period, no Hb values in the >12 to 13 g/dL range were reported for any subjects randomized to receive either vadadustat or placebo
- During the dose adjustment and maintenance period, Hb values in the >12 to 13 g/dL range were reported for 5 (11.4%) subjects in the vadadustat group, and 1 (7.1%) subject in the placebo group that switched to vadadustat

CONCLUSIONS

Overall, efficacy and safety results from the phase 2 studies of vadadustat support its continued development for patients with anemia due to CKD. Further investigation of daily doses of vadadustat from 150 to 600 mg in phase 3 trials for treatment of anemia in Japanese patients with NDD-CKD or DD-CKD is ongoing.

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