Results from Part A of the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial (GBT440-031), a Placebo-Controlled Randomized Study Evaluating Voxelotor (GBT440) in Adults and Adolescents with Sickle Cell Disease

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On behalf of all HOPE investigators

Disclosures

Consultant/advisory boards:

- Global Blood Therapeutics
- Bluebird Bio
- Protagonist

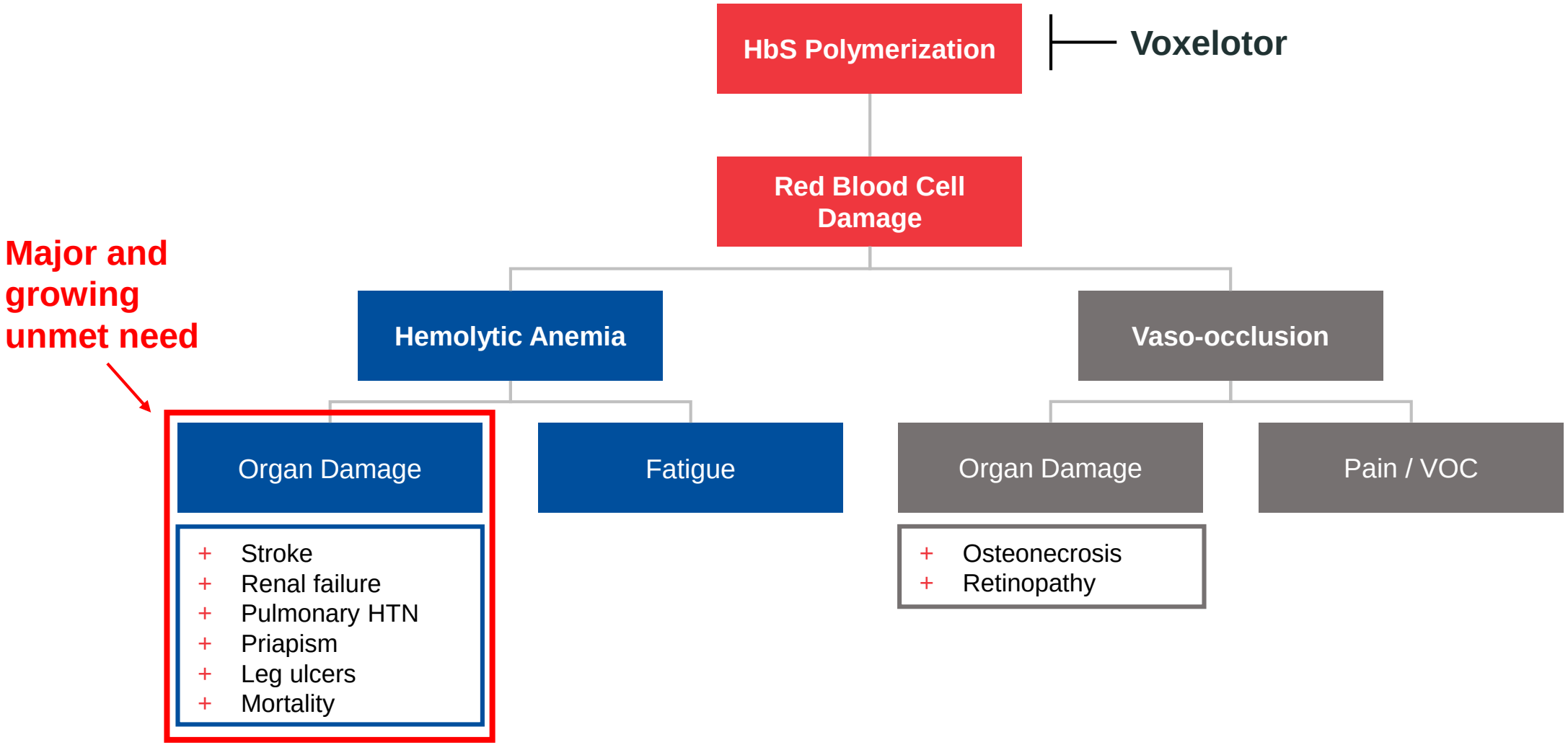
Voxelotor, a Novel Inhibitor of HbS Polymerization

- Novel mechanism that inhibits HbS polymerization and RBC sickling, the underlying pathophysiologic mechanism of SCD
- Preclinical and clinical studies to date demonstrated:
  - Improved red blood cell deformability and decreased blood viscosity[1]
  - Rapid, sustained, and clinically meaningful increases in Hb and reduction of hemolysis[2,3]
  - Favorable safety profile with once-daily oral dosing[2,3]
  - Improved blood oxygen carrying capacity and tissue oxygen delivery[4,5]
- Potential to modify morbidity and mortality by improving anemia and hemolysis

Hb, hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

1. Dufu K, et al. *Clin Hemorheol Microcirc*. 2018;70(1):95-105. 2. Lehrer-Graiwer, et al. ASH 2016. Poster/Abstract #2488. 3. Brown C, et al. EHA 2018. Poster/Abstract #PF709. 4. Smith G, et al. ATS 2018. Poster (hypoxic maximal conditions). 5. Smith G, et al. ATS 2018. Poster (submaximal hypoxic conditions).

Voxelotor Acts Upstream: Potential to be Disease Modifying



HTN, hypertension; VOC, vaso-occlusive crisis.
Adapted from Eaton WA, Bunn HF. *Blood* 2017;129(20):2719-2726.

HOPE Study Design—Part A

Key Eligibility Criteria

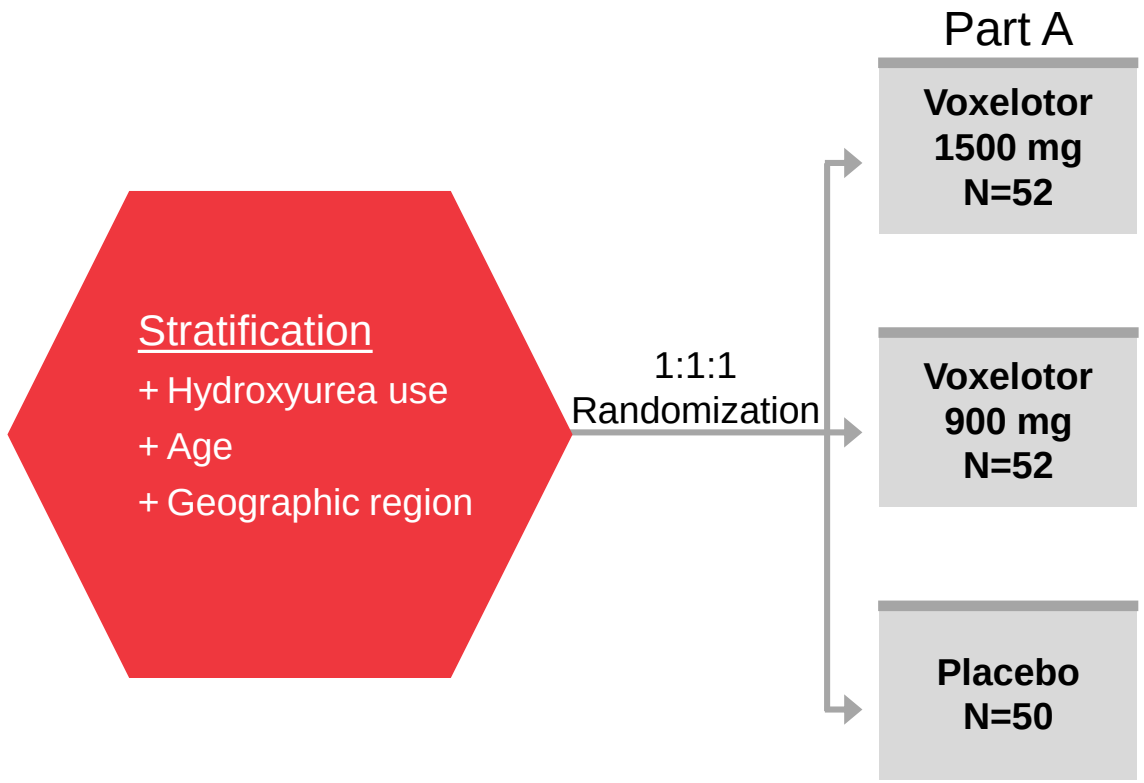
- 1-10 VOCs in prior year
- Hb ≥5.5 to ≤10.5 g/dL
- ≥12 years old
- Concomitant hydroxyurea allowed

Primary Endpoints

- Proportion of patients who achieve a >1 g/dL Hb improvement
- Safety

Key Secondary Endpoints

- Hemolysis measures
- VOC
- Patient-reported outcome



- Part A included 154 treated patients through Week 24
- Primary analysis of all patients (n=271) is planned in early 2019

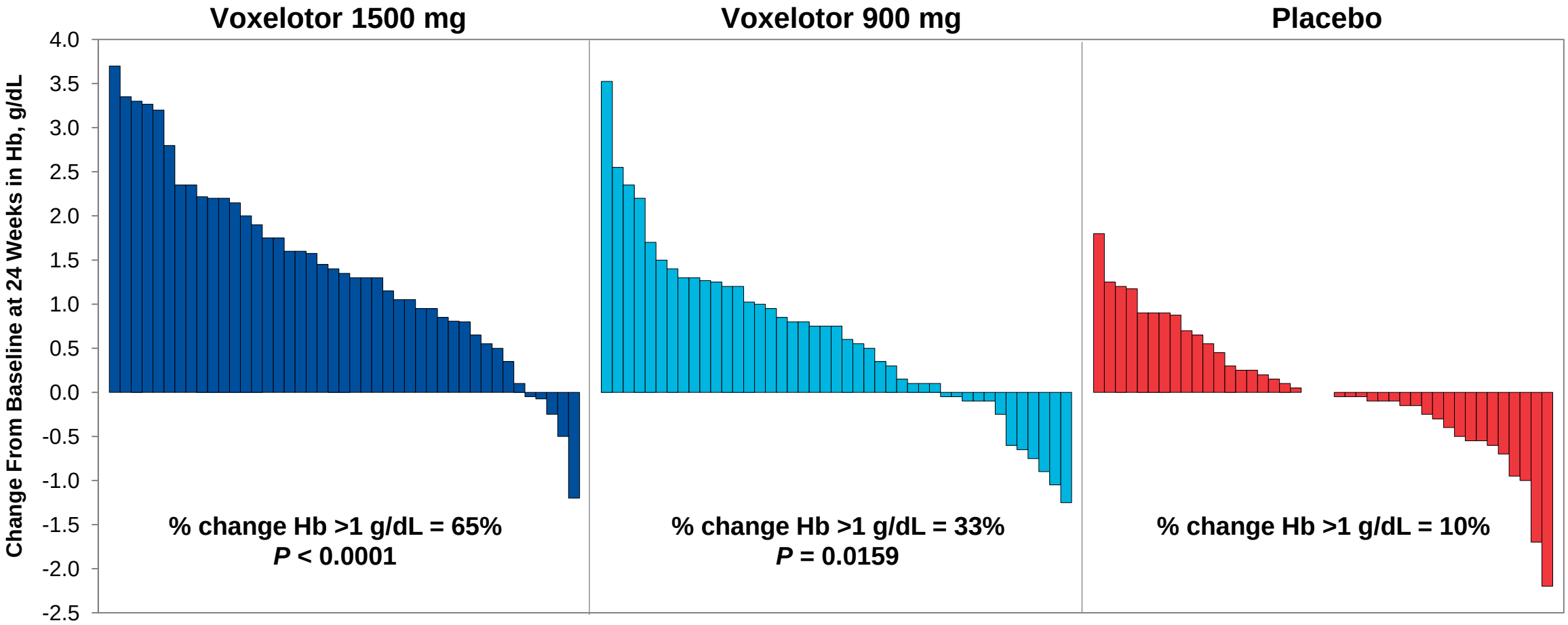
Data as of September 10, 2018.

Baseline Characteristics

Treatment	Voxelotor 1500 mg N=52	Voxelotor 900 mg N=52	Placebo N=50
Median age, years (range)	23 (12, 59)	26 (13, 59)	26 (12, 52)
12 to < 18 years, n (%)	8 (15)	7 (13)	6 (12)
18 to 65 years, n (%)	44 (85)	45 (87)	44 (88)
Male, n (%)	16 (31)	24 (46)	25 (50)
Region, n (%)			
North America	21 (40)	22 (42)	20 (40)
Europe	7 (13)	6 (12)	7 (14)
Other[a]	24 (46)	24 (46)	23 (46)
Genotype, n (%)			
HbSS/HbSβ^0 thalassemia	48 (92)	49 (94)	45 (90)
HbSC	1 (2)	1 (2)	2 (4)
Other[b]	3 (6)	2 (4)	3 (6)
Current hydroxyurea use, n (%)	32 (62)	35 (67)	32 (64)
Median baseline hemoglobin, g/dL (range)	8.6 (5.9, 10.8)	8.3 (6.3, 10.8)	8.5 (6.1, 10.4)
VOC episodes in previous 12 months,[c] n (%)			
1	23 (44)	21 (40)	22 (44)
2-5	25 (48)	27 (52)	24 (48)
6-10	4 (8)	4 (8)	4(8)

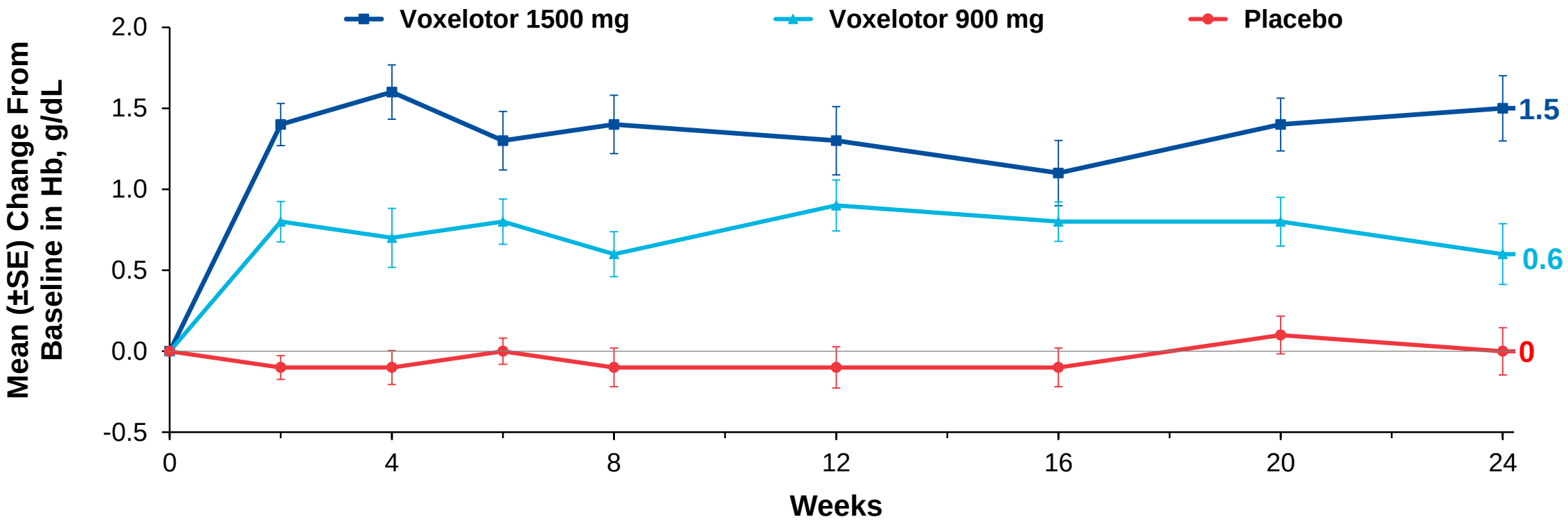
[a]Other regions: Lebanon, Turkey, Oman, Egypt, Kenya, Jamaica.
[b]Other genotypes include: HbSβ$^+$ thalassemia, other sickle cell syndrome variant.
[c]Baseline VOC defined as document episode of ACS or acute painful crisis that required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain.

65% of Patients Receiving Voxelotor 1500 mg Achieved >1 g/dL Increase in Hemoglobin



Baseline = average of screening and Day 1; 24 Weeks = average of Weeks 20 and 24. *P* values are based on comparison with placebo.

Voxelotor Demonstrates a Rapid, Robust, and Sustained Improvement in Anemia at Target Hemoglobin Occupancy

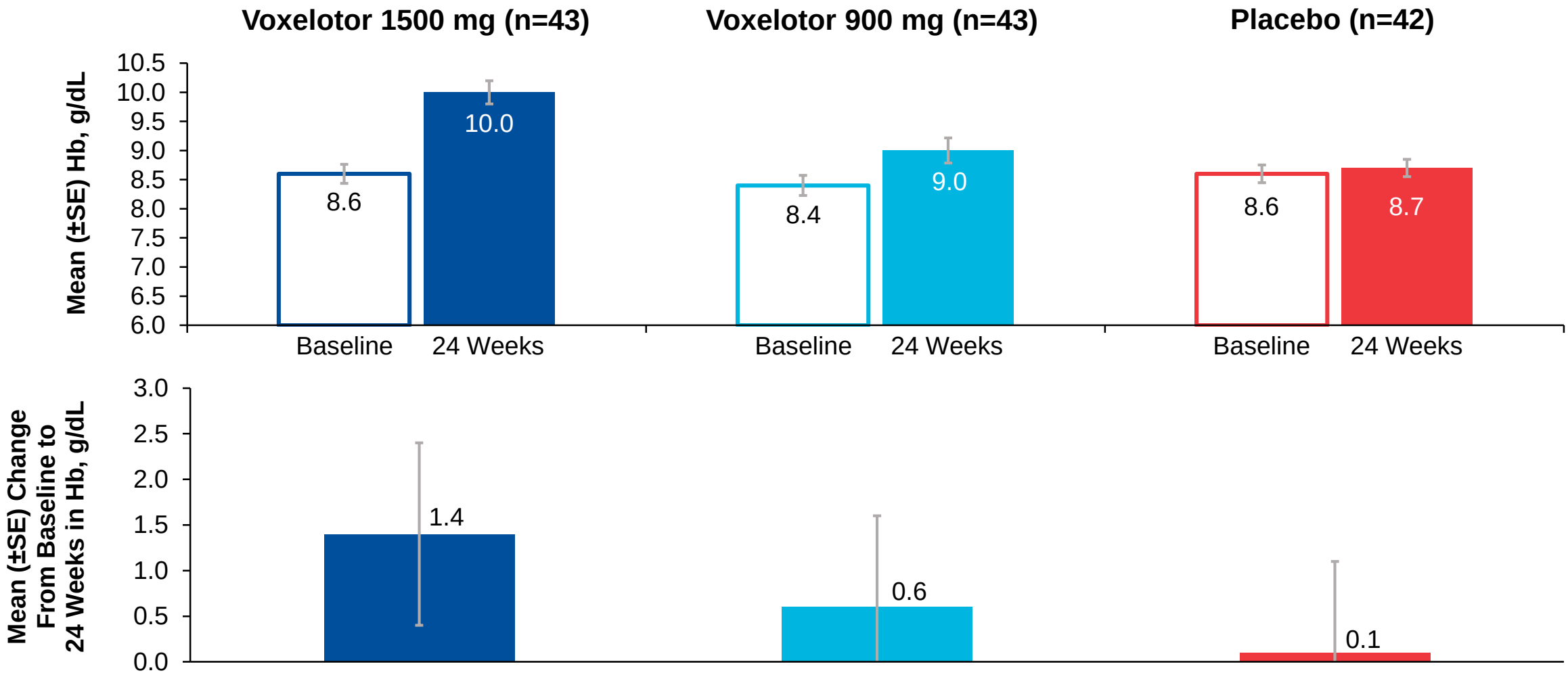


Value	Voxelotor 900 mg	Voxelotor 1500 mg
% Hb occupancy[a] (C_{min})	13.8% (46.5)	25.3% (32.8)

SE, standard error

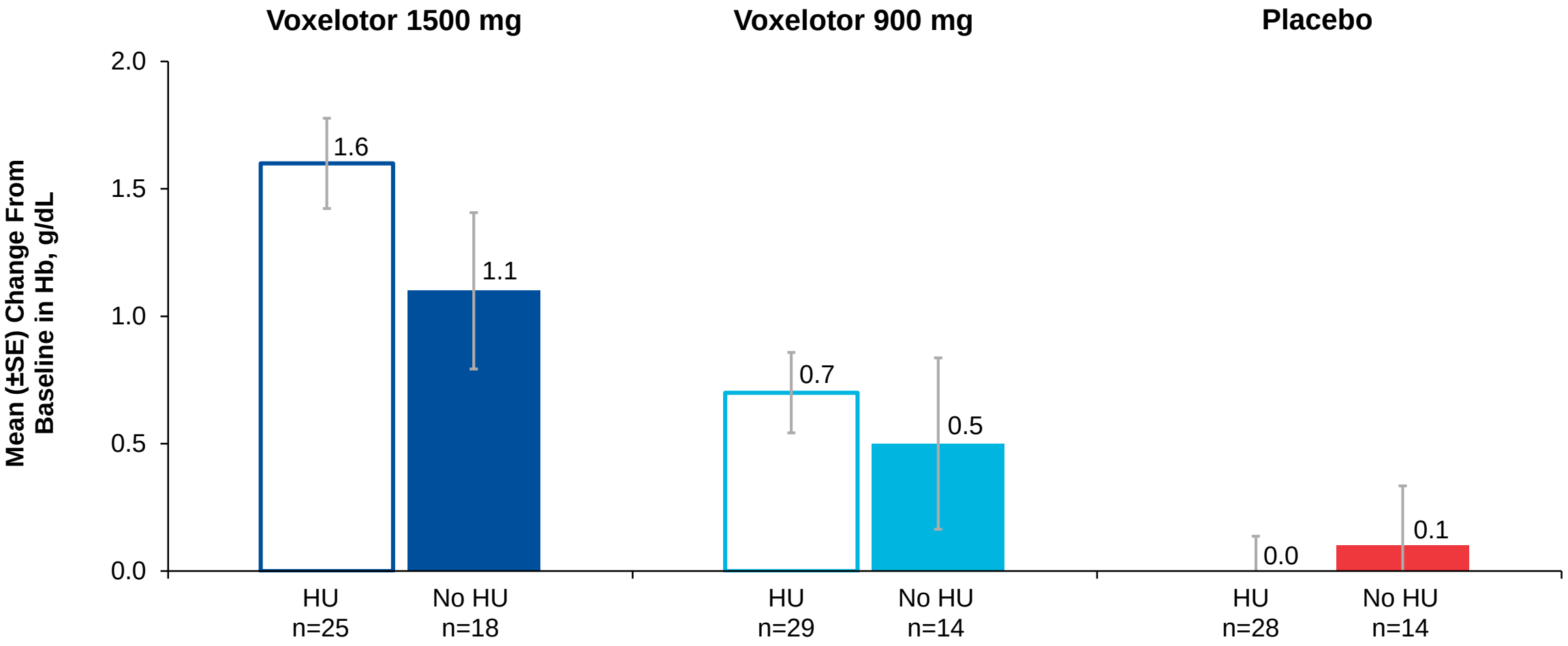
[a]Hb occupancy geometric mean (%CV) = calculated % of RBC Hb bound by voxelotor.

Voxelotor 1500 mg Increased Hemoglobin to Mean of 10 g/dL, Consistent With Substantial Improvement in Anemia



Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

Hemoglobin Improvement With or Without Hydroxyurea (HU)



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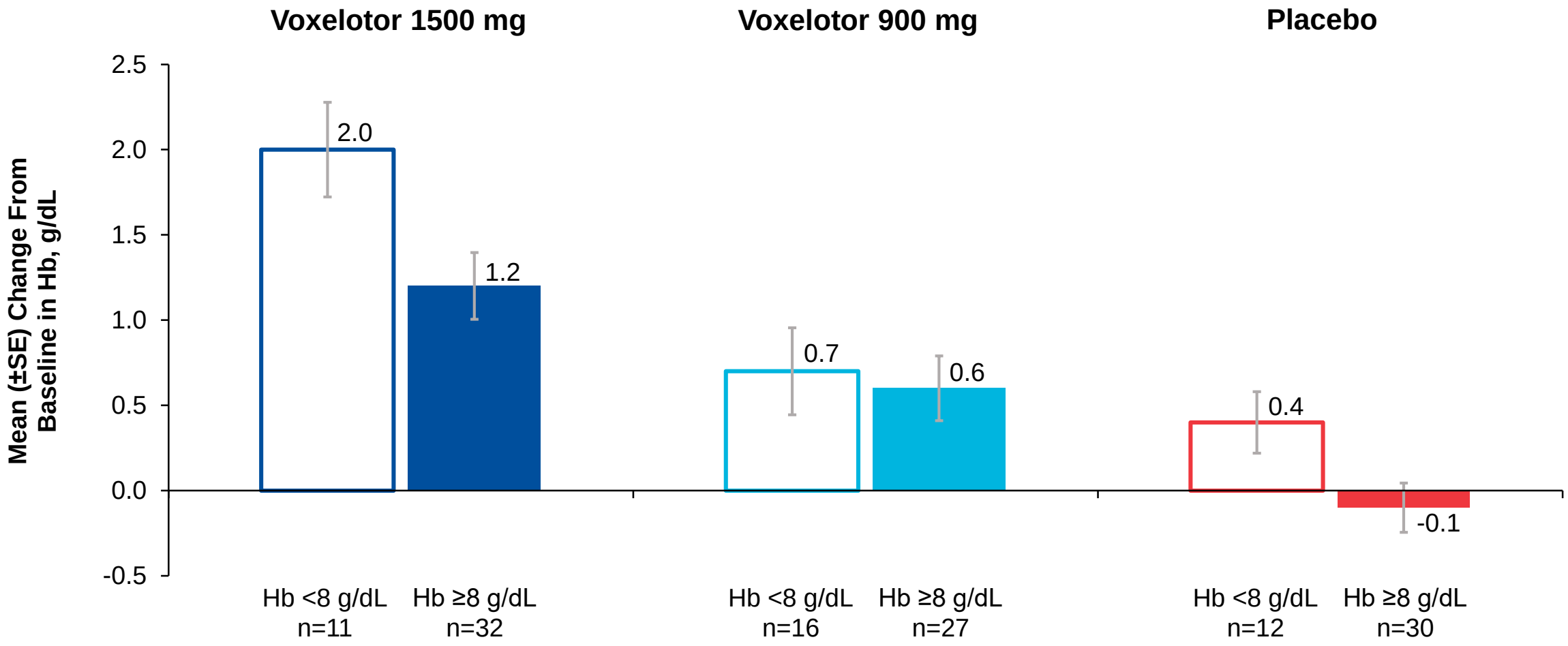
Hemoglobin Improvement Regardless of Baseline Anemia Severity



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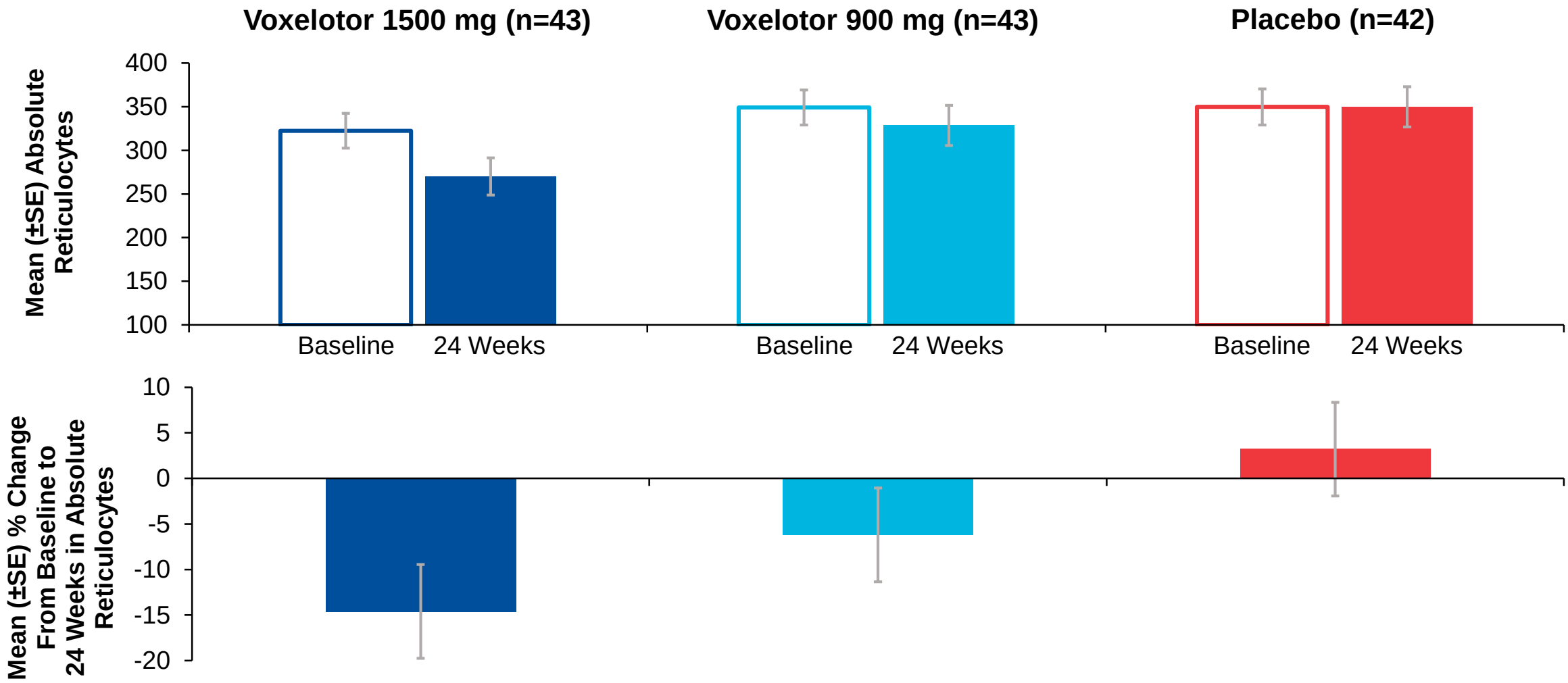
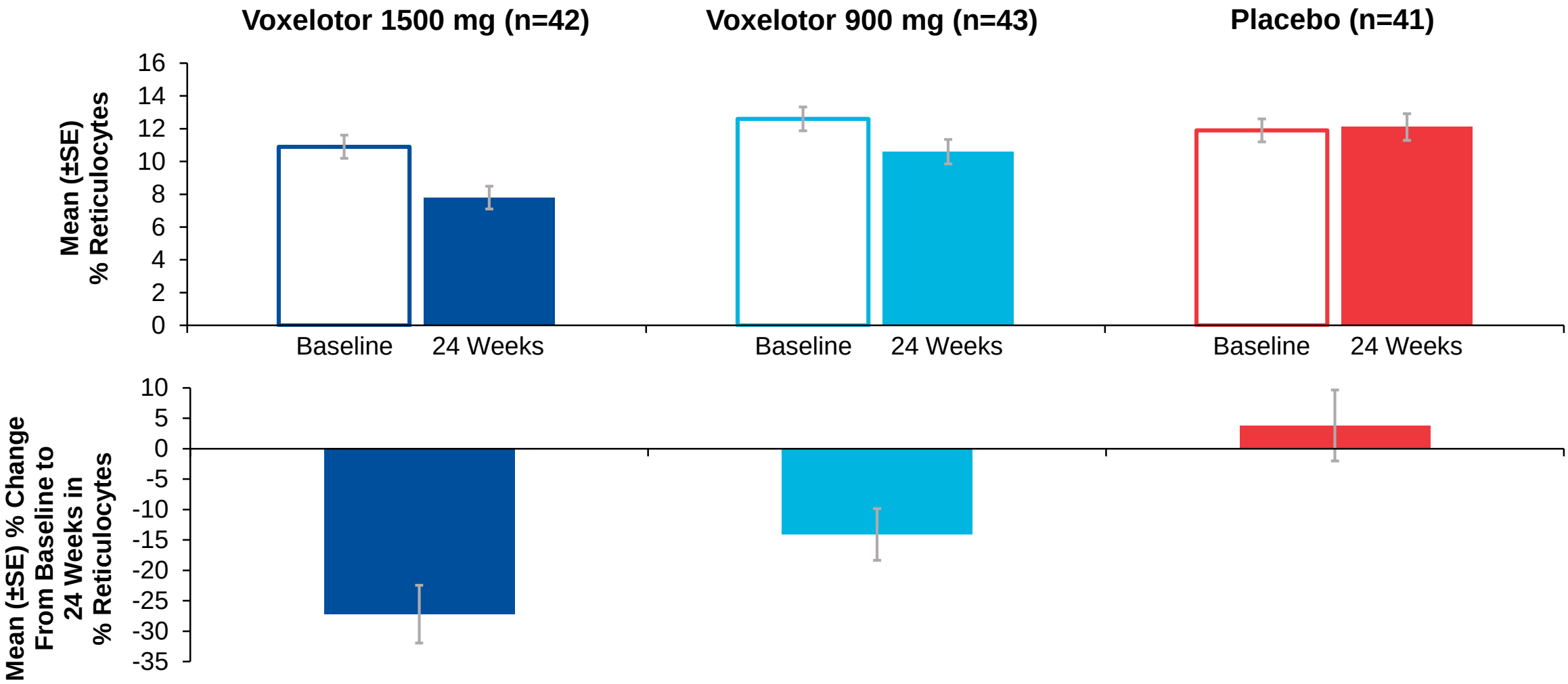
Absolute Reticulocyte Count Improvement Consistent With Decreased Hemolysis



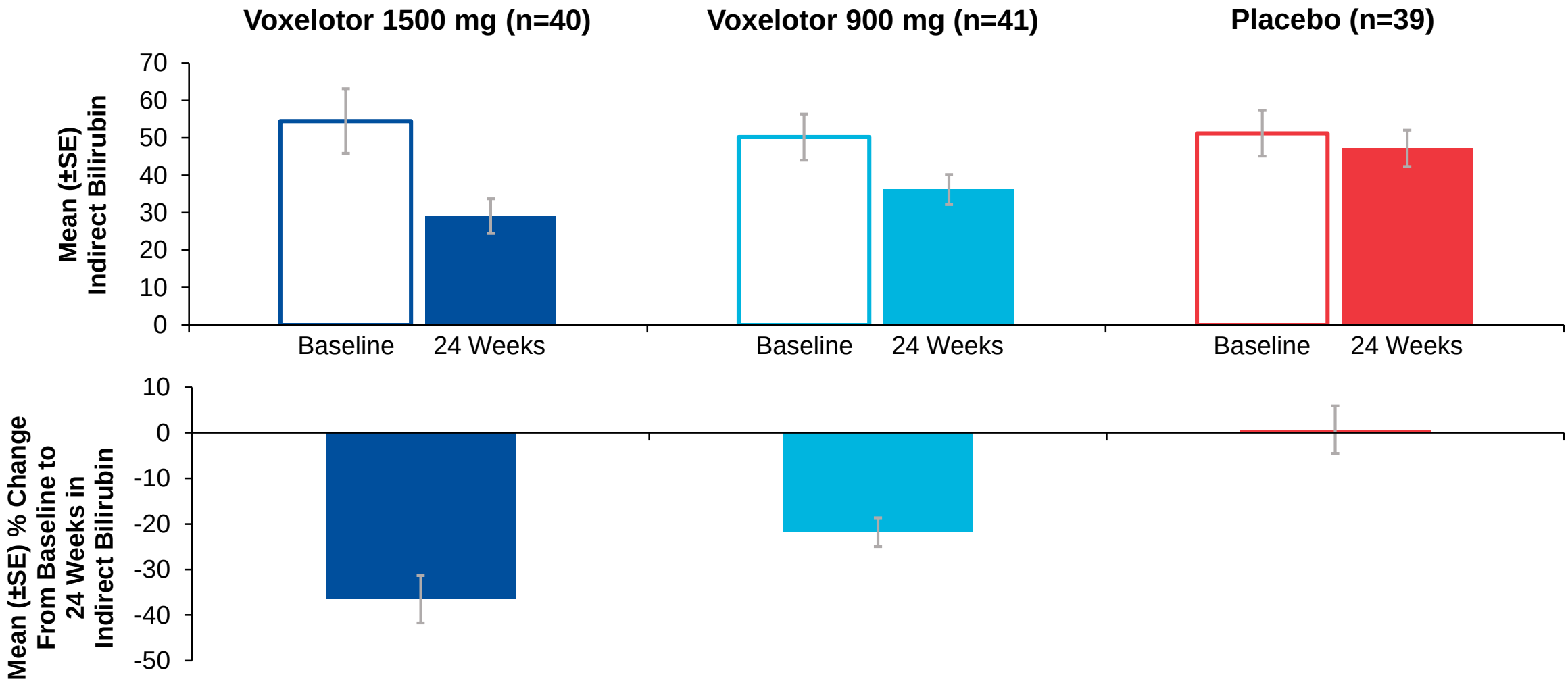
Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

Percent Reticulocyte Count Improvement Consistent With Decreased Hemolysis



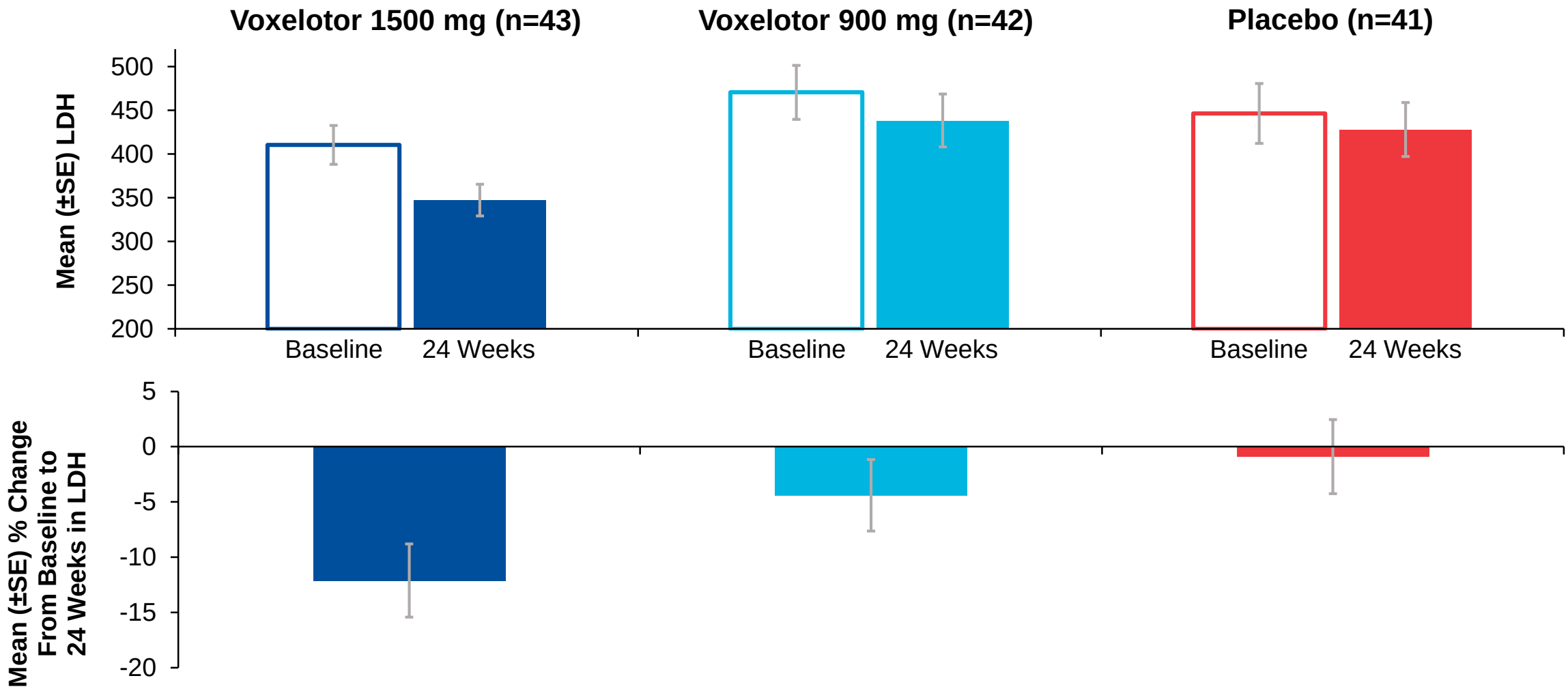
Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

Indirect Bilirubin Improvement Consistent With Decreased Hemolysis



Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

LDH Improvement Consistent With Decreased Intravascular Hemolysis



LDH, lactate dehydrogenase.
Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

Treatment-Emergent Adverse Events

	Voxelotor 1500 mg N=52	Voxelotor 900 mg N=52	Placebo N=50
Any AE	48 (92%)	46 (88%)	47 (94%)
Grade ≥3	29 (56%)	31 (60%)	27 (54%)
AE leading to treatment discontinuation	5 (10%)	3 (6%)	2 (4%)
SAE (not including VOC or ACS)	25 (48%)	29 (56%)	24 (48%)
Fatal SAE	0	0	1 (2%)

ACS, acute chest syndrome; AE, adverse event; SAE, serious adverse event.

Treatment-Emergent Adverse Events Occurring in ≥10% of Subjects

Preferred Term, n (%)	Voxelotor 1500 mg N=52	Voxelotor 900 mg N=52	Placebo N=50
Patients with ≥1 event (not including SCD events)	48 (92)	46 (88)	47 (94)
Diarrhea	11 (21)	10 (19)	5 (10)
Headache	15 (29)	6 (12)	13 (26)
Upper respiratory tract infection	7 (13)	11 (21)	5 (10)
Arthralgia	9 (17)	7 (13)	5 (10)
Nausea	8 (15)	8 (15)	6 (12)
Abdominal pain	7 (13)	6 (12)	4 (8)
Fatigue	5 (10)	7 (13)	6 (12)
Pain	5 (10)	7 (13)	4 (8)
Vomiting	7 (13)	5 (10)	7 (14)
Back pain	5 (10)	6 (12)	4 (8)
Pain in extremity	4 (8)	7 (13)	8 (16)
Pyrexia	4 (8)	6 (12)	2 (4)
Pneumonia	3 (6)	6 (12)	6 (12)
Urinary tract infection	5 (10)	4 (8)	7 (14)
Cough	5 (10)	2 (4)	3 (6)

Fewer VOC With Substantial Increase in Hemoglobin

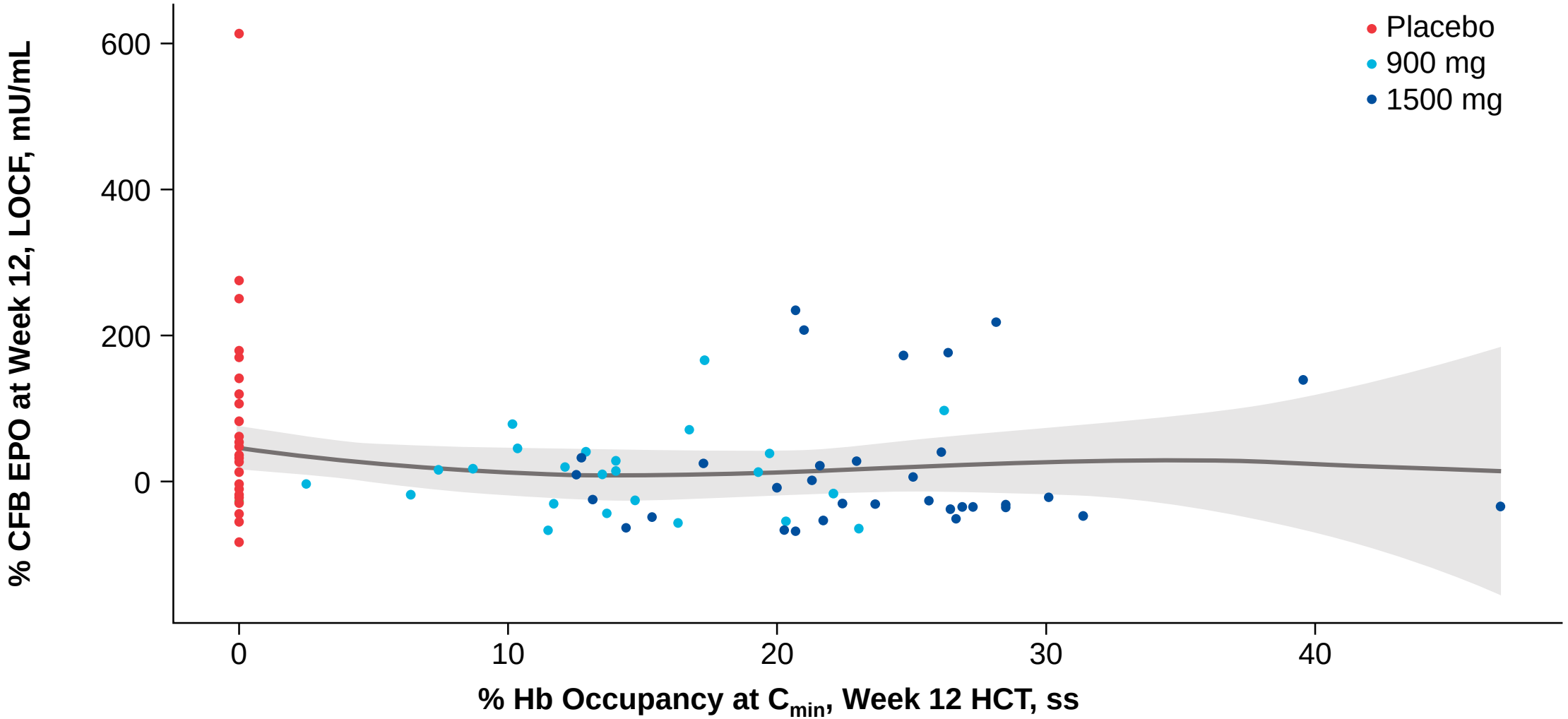
	Voxelotor 1500 mg N=52	Voxelotor 900 mg N=52	Placebo N=50
No. of VOC (No. of participants with ≥1 VOC)	109 (36)	113 (34)	131 (35)
VOC incidence (per person-year)	2.77	2.85	3.41

VOC definition includes ACS

- Moderate to severe pain lasting ≥2 hours
- No explanation other than VOC
- Requires medication prescribed/directed by a healthcare professional
- Patient was seen in medical facility or contacted site within 1 business day

Median follow up = 41.6 weeks for all patients (N=154)

No Treatment-Related Increase in Erythropoietin, Indicating Preserved Tissue Oxygenation



CFB, change from baseline; EPO, erythropoietin; HCT, hematocrit; LOCR, last observation carried forward

Conclusions

- Rapid, robust, and sustained improvement in hemoglobin and hemolysis
- Voxelotor 1500 mg dose demonstrated:
  - Hemoglobin increase of >1 g/dL in 65% of patients
  - Anemia improvement irrespective of baseline anemia severity or HU use
- Voxelotor was safe and well tolerated
- Fewer VOC with substantial increase in hemoglobin
- Preserved tissue oxygenation as indicated by reduction in reticulocyte counts and stable erythropoietin levels

Voxelotor has the potential to modify the morbidity of chronic organ damage associated with SCD by improving anemia and hemolysis

Thank You to All the HOPE Investigators

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*Indicates change of Principal Investigator

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