Disclosures

Consultant/advisory boards:

- Global Blood Therapeutics, Inc.
- Imara, Inc.

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- Novartis
- Terumo

Results From the Randomized, Placebo-Controlled, Phase 3 Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial of Voxelotor in Adults and Adolescents With Sickle Cell Disease

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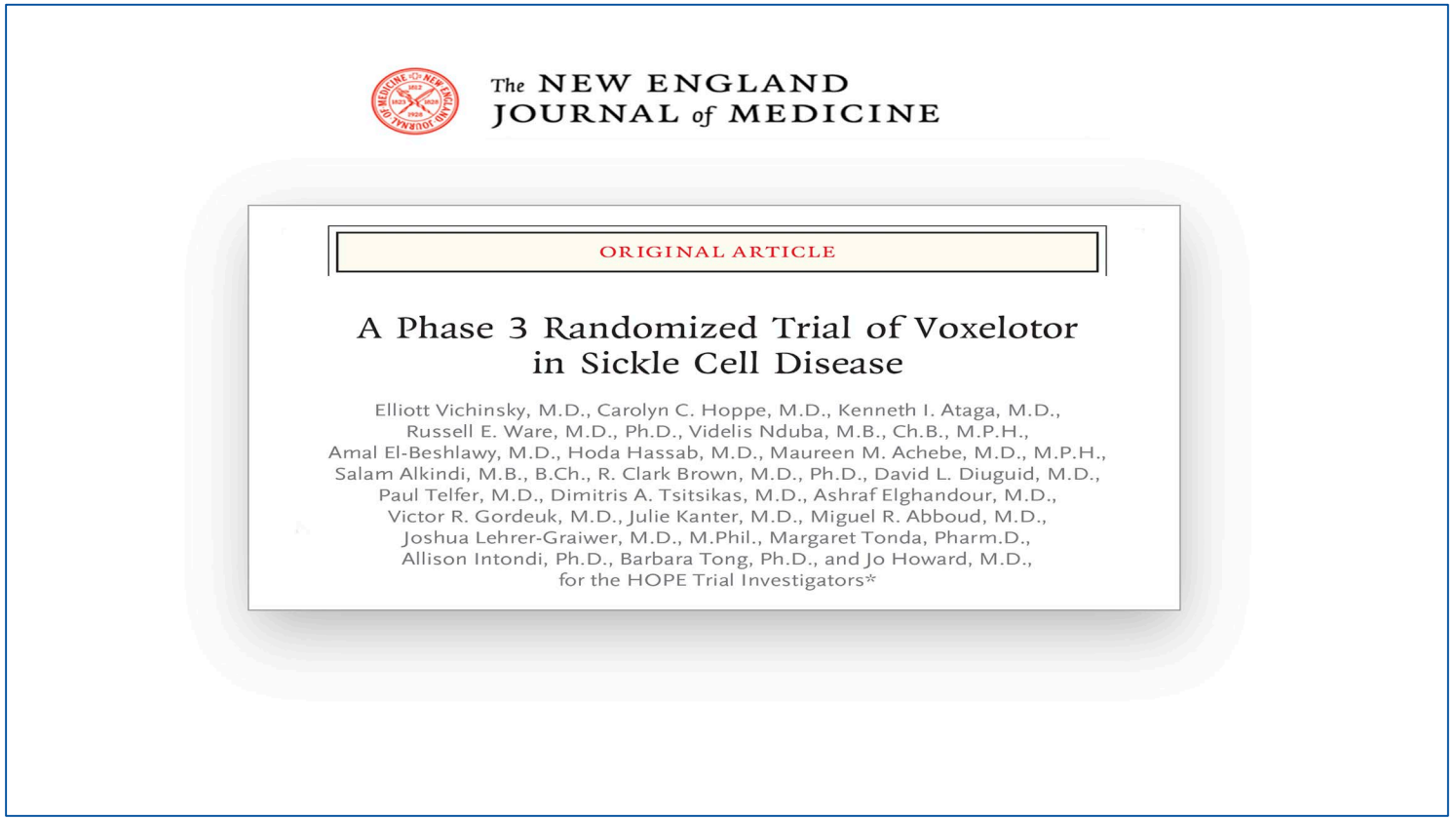
On behalf of all HOPE investigators

This Study Is Now Published in *NEJM*

- The manuscript was published online this morning by *The New England Journal of Medicine* www.nejm.org/doi/full/10.1056/NEJMoa1903212



Voxelotor Is a First-in-Class HbS Polymerization Inhibitor

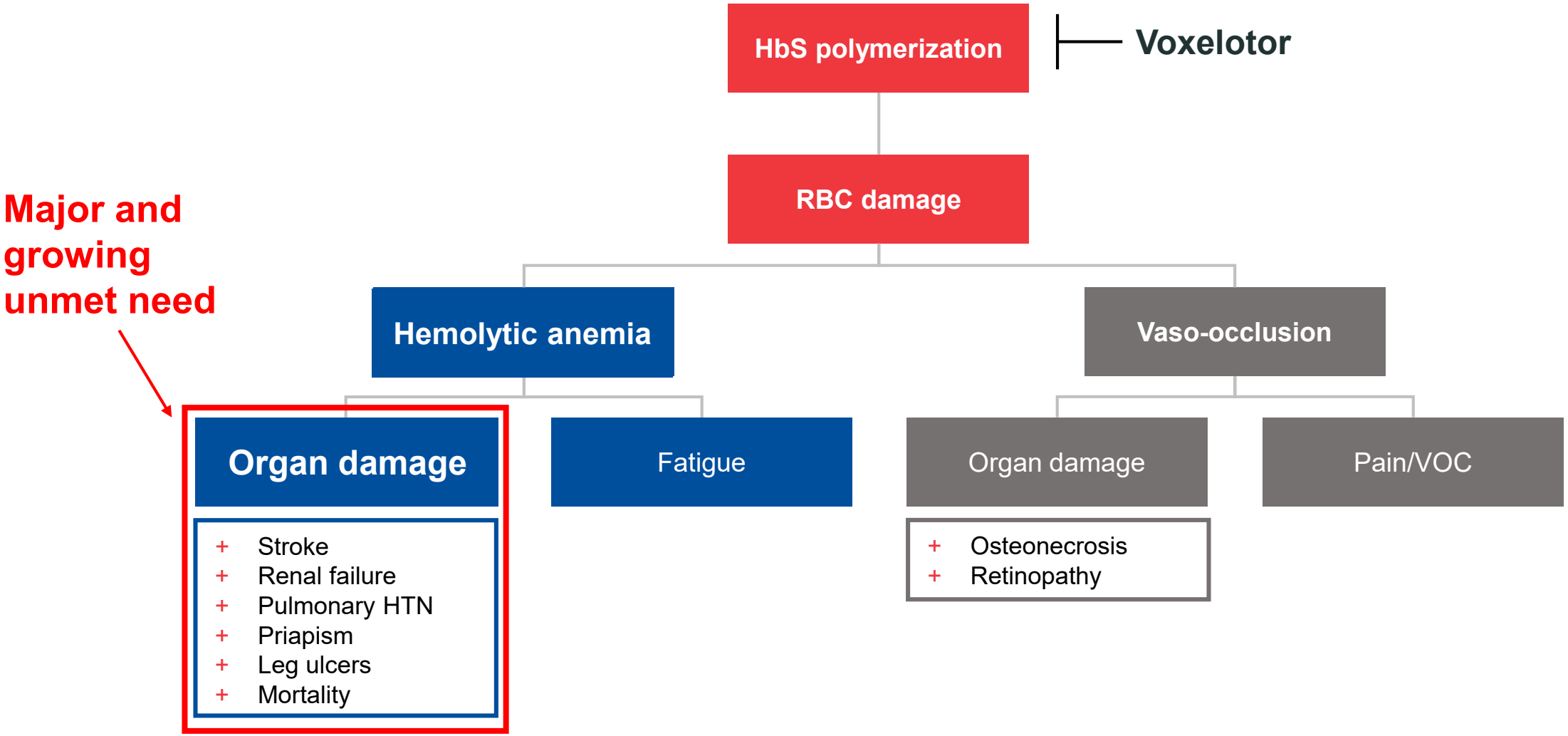
- Novel small molecule that inhibits HbS polymerization and RBC sickling, the underlying molecular basis of SCD[1]

- Preclinical and clinical studies to date showed:
  - Improved RBC 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]

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

1. Dufu K, *et al. Clin Hemorheol Microcirc*. 2018;70:95–105. 2. Howard J, *et al. Blood*. 2019;133:1865–1875. 3. Brown C, *et al.* Presented at the 24th Annual Meeting of The European Hematology Association; June 14–16, 2018; Stockholm, Sweden. Poster PF709. 4. Stewart G, *et al.* Presented at the Annual Meeting of the American Thoracic Society; May 18–23, 2018; San Diego, CA. Poster A2367. 5. Stewart G, *et al.* Presented at the Annual Meeting of the American Thoracic Society; May 18–23, 2018; San Diego, CA. A2368.

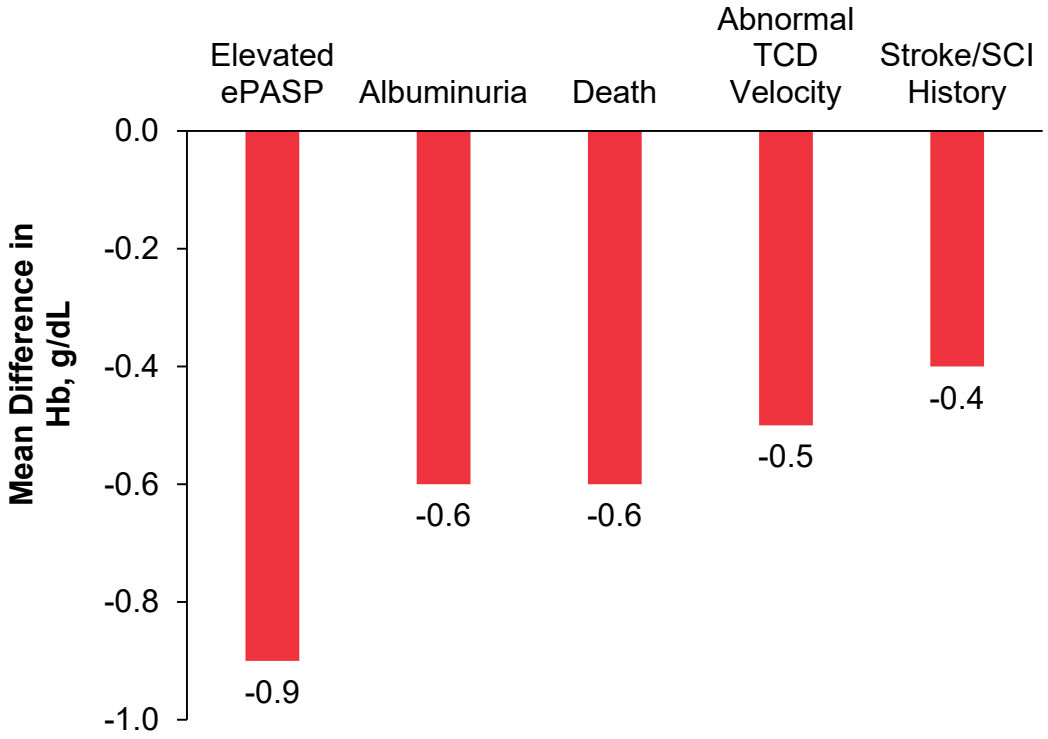
Voxelotor Acts Upstream: Potential to Be Disease Modifying



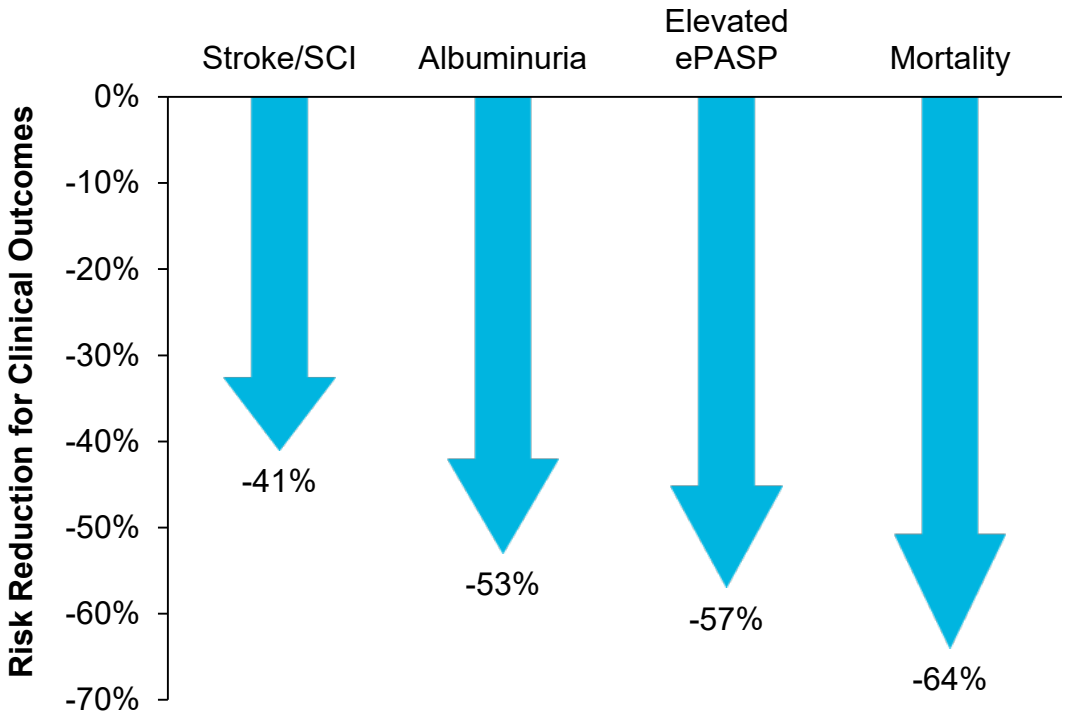
HbS, sickle hemoglobin; HTN, hypertension; RBC, red blood cell; VOC, vaso-occlusive crisis.
Adapted from Eaton WA, Bunn HF. *Blood.* 2017;129:2719–2726.

Increase in Hb Is Likely to Predict Clinical Benefit[1,2]

- Lower Hb levels are associated with negative clinical outcomes



- Improvement in Hb of ≥1 g/dL can potentially reduce clinical complications and mortality



ePASP, estimated pulmonary arterial systolic pressure; Hb, hemoglobin; SCD, sickle cell disease; SCI, silent cerebral infarct; TCD, transcranial Doppler.

1. Ataga KI, *et al. Blood.* 2018;132:12. 2. Ataga KI, *et al.* Presented at the 2019 American Society of Pediatric Hematology/Oncology (ASPHO) Conference; May 1–4, 2019; New Orleans, LA. Poster 718.

The HOPE Study Evaluated Voxelotor 1500 mg and 900 mg Daily vs Placebo in Adults and Adolescents With SCD

Key Eligibility Criteria

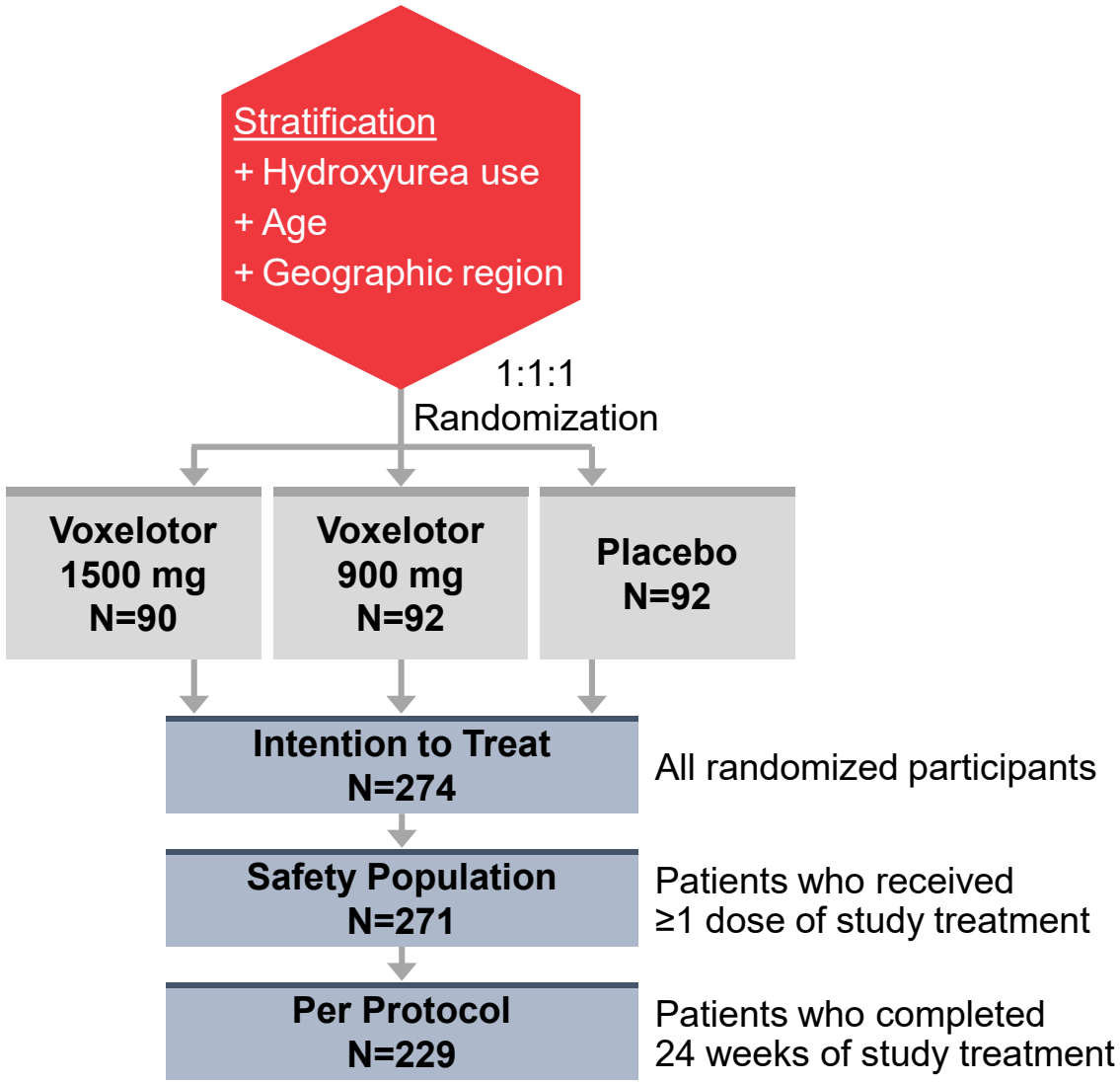
- Hb 5.5–10.5 g/dL
- 1–10 VOCs in prior 12 months
- Aged 12–65 years
- Concomitant hydroxyurea allowed
- Confirmed SCD (eligible genotypes: HbSS, $HbS\beta^0$, $HBS\beta^+$, and HbSC)

Primary Endpoint

- Proportion of patients with >1.0 g/dL Hb increase at 24 weeks
- Safety

Key Secondary Endpoints

- Hemolysis measures, change from baseline to week 24
- Hb, change from baseline to week 24
- VOC, final analysis at 72 weeks



Data as of October 31, 2018.
Hb, hemoglobin; HbSC, heterozygous for SCD; HbSS, sickle cell anemia; HbSβ, sickle cell beta thalassemia; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Baseline Characteristics Were Generally Well Balanced

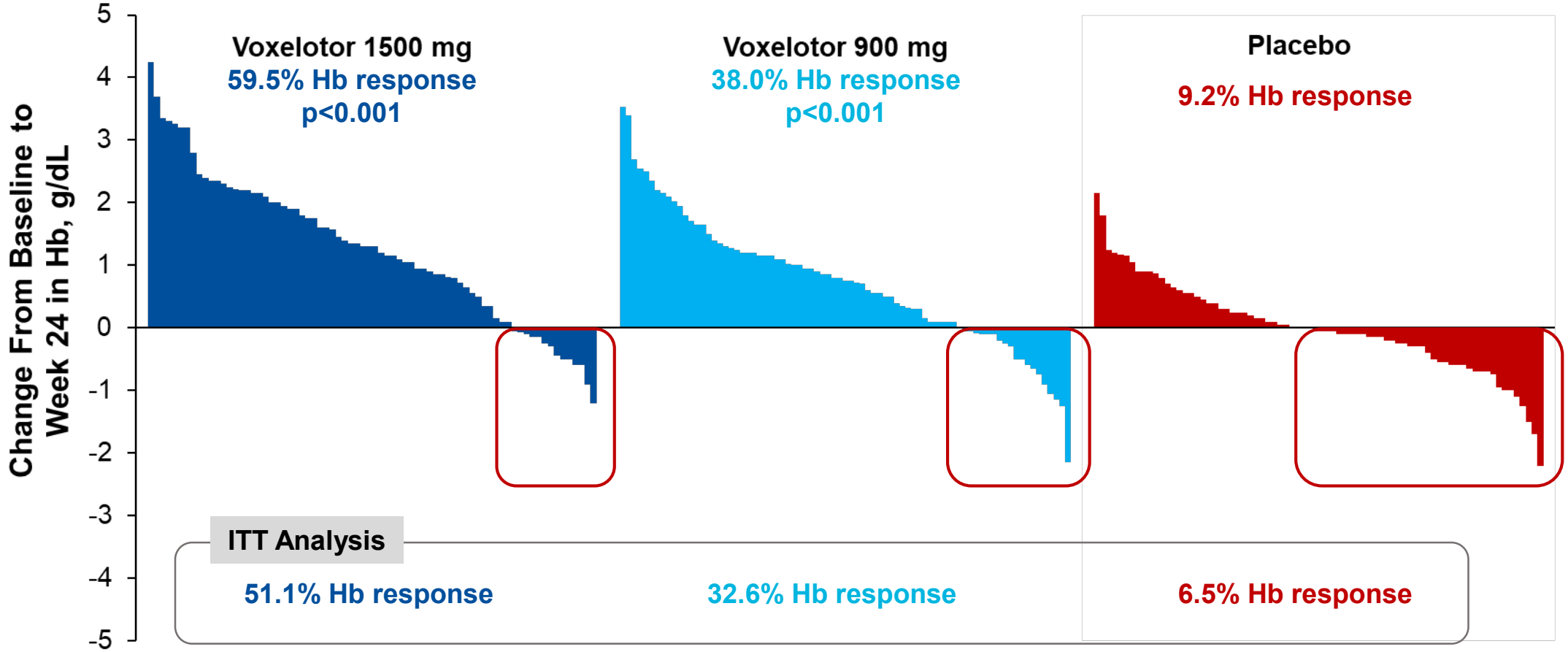
Treatment	Voxelotor 1500 mg N=90	Voxelotor 900 mg N=92	Placebo N=92
Median age, years (range)	24 (12–59)	24 (12–59)	28 (12–64)
12 to <18 years, n (%)	14 (15.6)	15 (16.3)	17 (18.5)
18 to 65 years, n (%)	76 (84.4)	77 (83.7)	75 (81.5)
Female, n (%)	58 (64.4)	51 (55.4)	50 (54.3)
Region, n (%)			
North America	34 (37.8)	36 (39.1)	35 (38.0)
Europe	19 (21.1)	19 (20.7)	18 (19.6)
Other[a]	37 (41.1)	37 (40.2)	39 (42.4)
Genotype, n (%)			
HbSS	61 (67.8)	71 (77.2)	74 (80.4)
HbSβ^0 thalassemia	18 (20.0)	13 (14.1)	11 (12.0)
HbSC	3 (3.3)	2 (2.2)	2 (2.2)
Other[b]	8 (8.9)	6 (6.5)	5 (5.5)
Patients on baseline hydroxyurea, n (%)	58 (64.4)	63 (68.5)	58 (63.0)
Median baseline Hb, g/dL (range)	8.7 (5.9–10.8)	8.3 (5.9–10.8)	8.6 (6.1–10.5)
VOC episodes in previous 12 months,[c] n (%)			
1	35 (38.9)	41 (44.6)	39 (42.4)
2–10	55 (61.1)	51 (55.4)	53 (57.6)
Median follow-up, weeks (range)	42.3 (0.1–73.3)	38.1 (4.0–72.4)	37.2 (8.1–72.9)

[a]Other regions: regions outside of North America or Europe. [b]Other genotypes include: HbSβ$^+$, other SCD variants. [c]Baseline VOC defined as documented episode of ACS or acute painful crisis that required prescription or healthcare professional–instructed use of analgesics for moderate to severe pain.
ACS, acute chest syndrome; Hb, hemoglobin; HbSC, heterozygous for SCD; HbSS, sickle cell anemia; HbSβ, sickle cell beta thalassemia; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

RESULTS

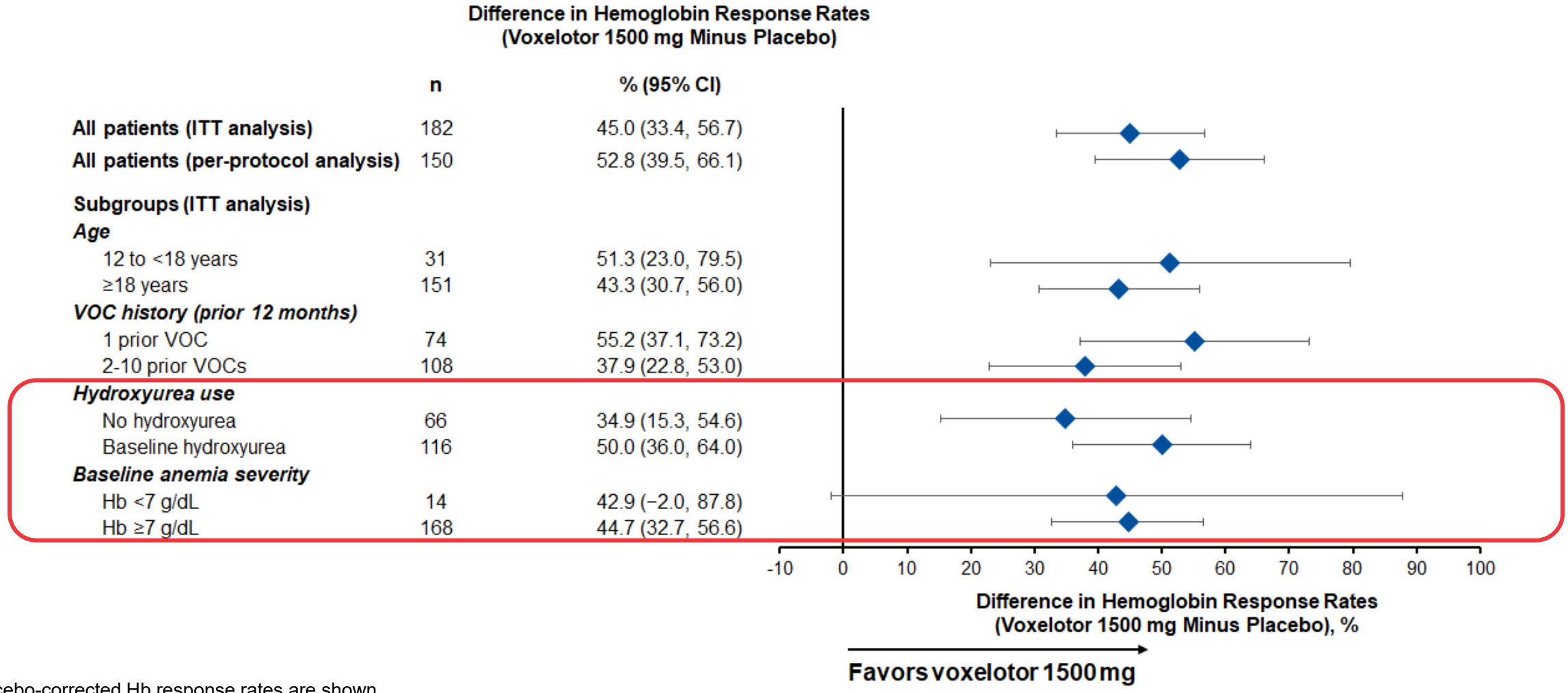
59.5% of Patients Achieved an Increase >1 g/dL Hb*

Over 80% of Patients Receiving Voxelotor 1500 mg Had an Increase in Hb



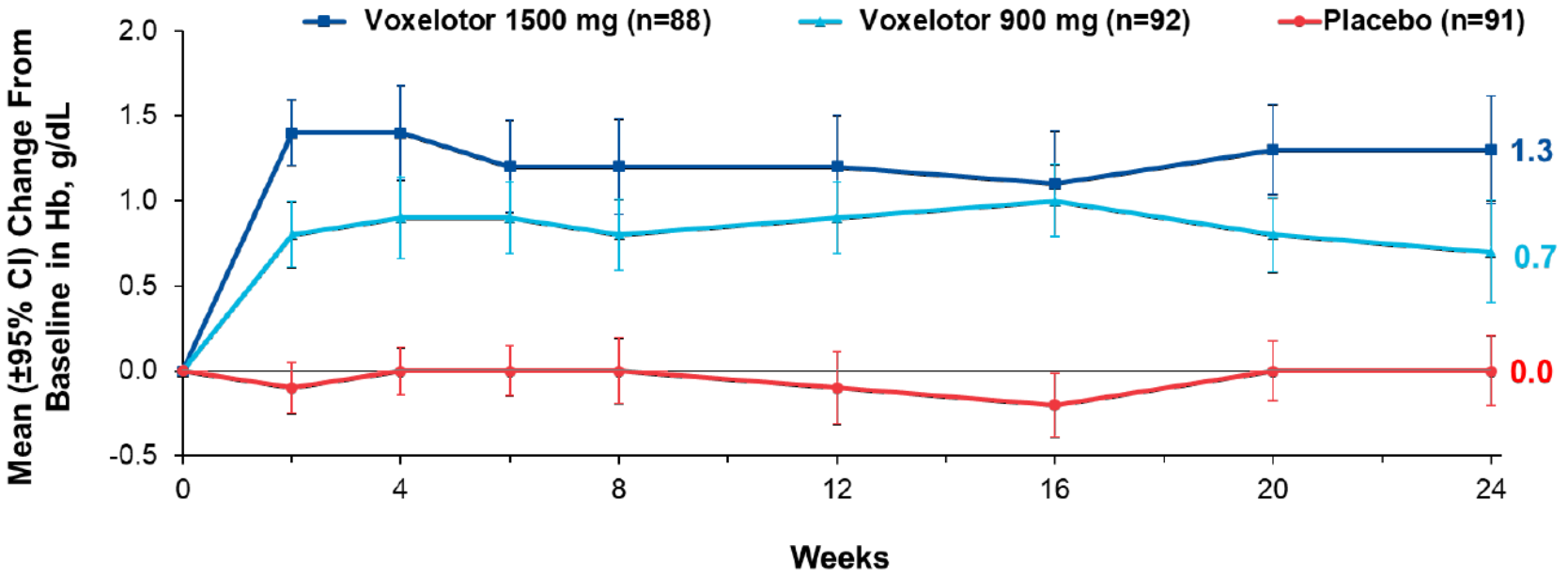
Baseline = average of screening and day 1; 24 weeks = average of weeks 20 and 24.
*Hb response is defined as a >1 g/dL increase in Hb. Per-protocol analysis. The primary reason for the difference in response rates between analyses is that participants who did not complete the primary endpoint visit of 24 weeks are considered non-responses in the Hb response analysis. Hb, hemoglobin; ITT, intention-to-treat.

Voxelotor 1500 mg Daily Showed Robust and Consistent Placebo-Corrected Hb Response Rates Across Subgroups



Placebo-corrected Hb response rates are shown.
Baseline = average of screening and day of randomization; 24 weeks = average of weeks 20 and 24.
CI, confidence interval; Hb, hemoglobin; ITT, intention-to-treat; VOC, vaso-occlusive crisis.

Voxelotor Demonstrates a Rapid, Robust, and Sustained Improvement in Anemia



No. of Patients								
Voxelotor 1500 mg	76	78	72	70	68	72	70	69
Voxelotor 900 mg	80	77	66	73	75	74	71	77
Placebo	81	78	77	70	77	75	73	68

ITT Analysis

1.1 g/dL Hb

0.6 g/dL Hb

-0.1 g/dL Hb

P<0.001

The mean change in Hb (±95% CI) from baseline to week 24 in the per-protocol analysis of observed data is presented. Total n represents the number of participants with any post-baseline observations; the sample sizes vary over time. Laboratory values obtained after hydroxyurea was initiated post-randomization were excluded for participants who were not using hydroxyurea at baseline (n=4 [n=1 for 1500 mg; n=3 for placebo]). Laboratory values after last dose were excluded.
CI, confidence interval; Hb, hemoglobin.

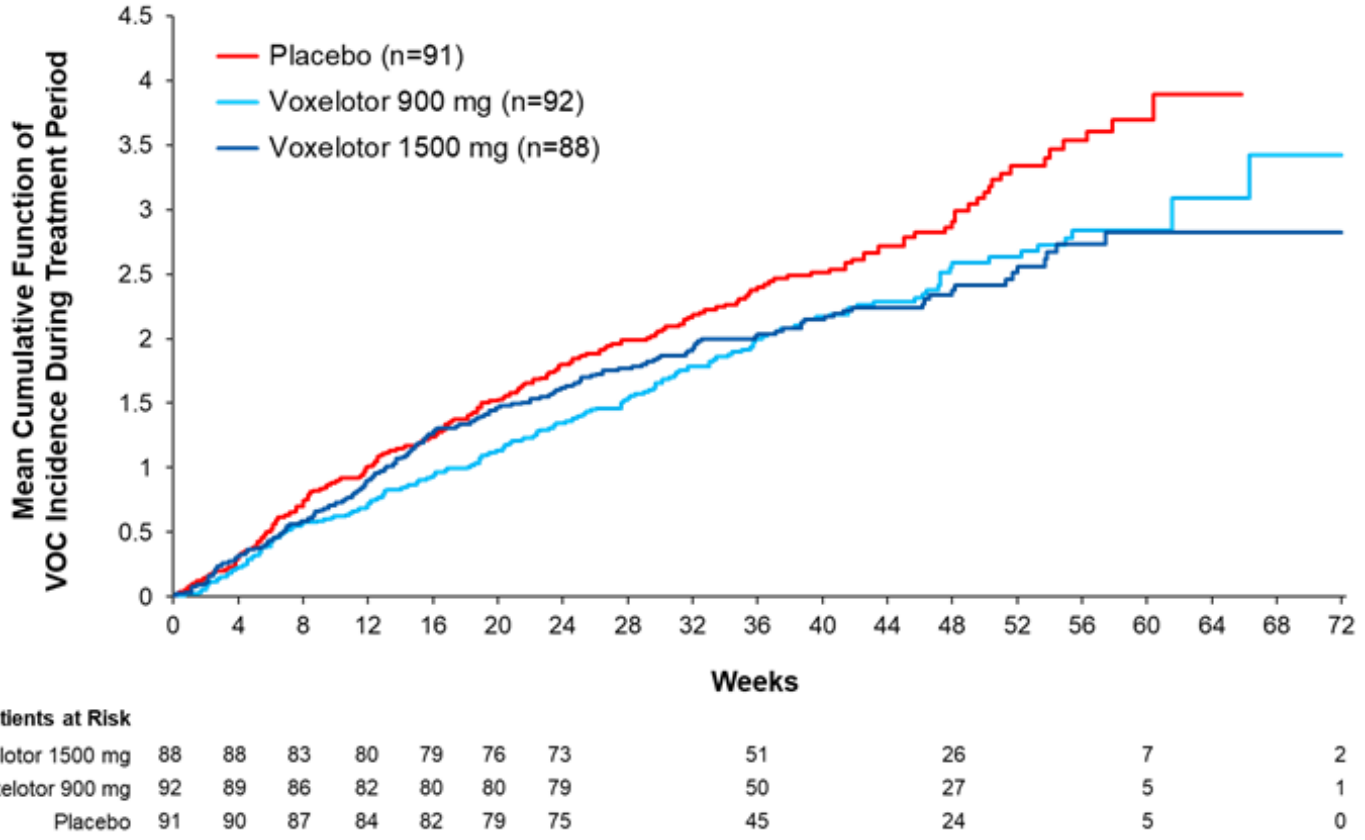
Voxelotor 1500 mg Decreased Markers of Hemolysis Compared With Placebo

	Voxelotor 1500 mg Occupancy 26.5%	Voxelotor 900 mg Occupancy 17.1%	Placebo
% change in indirect bilirubin (95% CI)	**−29.1** (−35.9, −22.2)	**−20.3** (−27.1, −13.6)	−3.2 (−10.1, 3.8)
% change in reticulocytes % (95% CI)	**−19.9** (−29.0, −10.9)	−1.3 (−10.3, 7.7)	4.5 (−4.5, 13.6)
% change in absolute reticulocytes (95% CI)	−8.0 (−18.1, 2.1)	5.1 (−4.9, 15.2)	3.1 (−7.0, 13.2)
% change in LDH (95% CI)	−4.5 (−11.9, 2.8)	1.4 (−5.9, 8.7)	3.4 (−4.0, 10.9)

Least squares mean change from baseline to week 24, where baseline is defined as the average of screening and day 1. All n values shown represent the number of participants who contributed any observations to the regression model for repeated measures. Bolded values represent significant differences from placebo; testing of voxelotor 900-mg group vs placebo is exploratory in nature. CI, confidence interval; LDH, lactate dehydrogenase.

Fewer VOCs With Substantial Increase in Hb

	Voxelotor 1500 mg N=88	Voxelotor 900 mg N=92	Placebo N=91
Number of VOCs (participants with ≥1 VOC)	179 (59)	183 (61)	219 (63)
VOC incidence, per person-year, unadjusted (95% CI)	2.76 (2.37, 3.20)	2.73 (2.35, 3.15)	3.42 (2.98, 3.90)
VOC incidence, per person-year, adjusted[a] (95% CI)	2.77 (2.15, 3.57)	2.76 (2.15, 3.53)	3.19 (2.50, 4.07)



[a]Adjusted for baseline hydroxyurea use, age group, and geographic region.
VOC definition includes ACS with moderate to severe pain lasting ≥2 hours, no explanation other than VOC, requires medication prescribed/directed by a healthcare professional, and patient was seen in medical facility or contacted site within 1 business day.
Final VOC analysis will be conducted at the end of study (72 weeks).
ACS, acute chest syndrome; CI, confidence interval; Hb, hemoglobin; VOC, vaso-occlusive crisis.

Rates of TEAEs, Grade ≥3 TEAEs, and Discontinuations Were Similar Between Patients Receiving Voxelotor and Placebo

Non-SCD-Related TEAE[a]	Voxelotor 1500 mg N=88	Voxelotor 900 mg N=92	Placebo N=91
Patients with ≥1 non-SCD-related TEAE (%)	83 (94.3)	86 (93.5)	81 (89.0)
Grade ≥3	23 (26.1)	21 (22.8)	24 (26.4)
Patients with ≥1 treatment-related TEAE[b]	34 (38.6)	29 (31.5)	23 (25.3)
Patients with serious TEAE[b] (%)	17 (19.3)	16 (17.4)	15 (16.5)
Treatment-related serious TEAE[b]	3 (3.4)	3 (3.3)	1 (1.1)
Patients with TEAE[b] leading to treatment discontinuation[c] (%)	8 (9.1)	5 (5.4)	4 (4.4)
Fatal serious TEAE[d] (%)	1 (1.1)	1 (1.1)	2 (2.2)

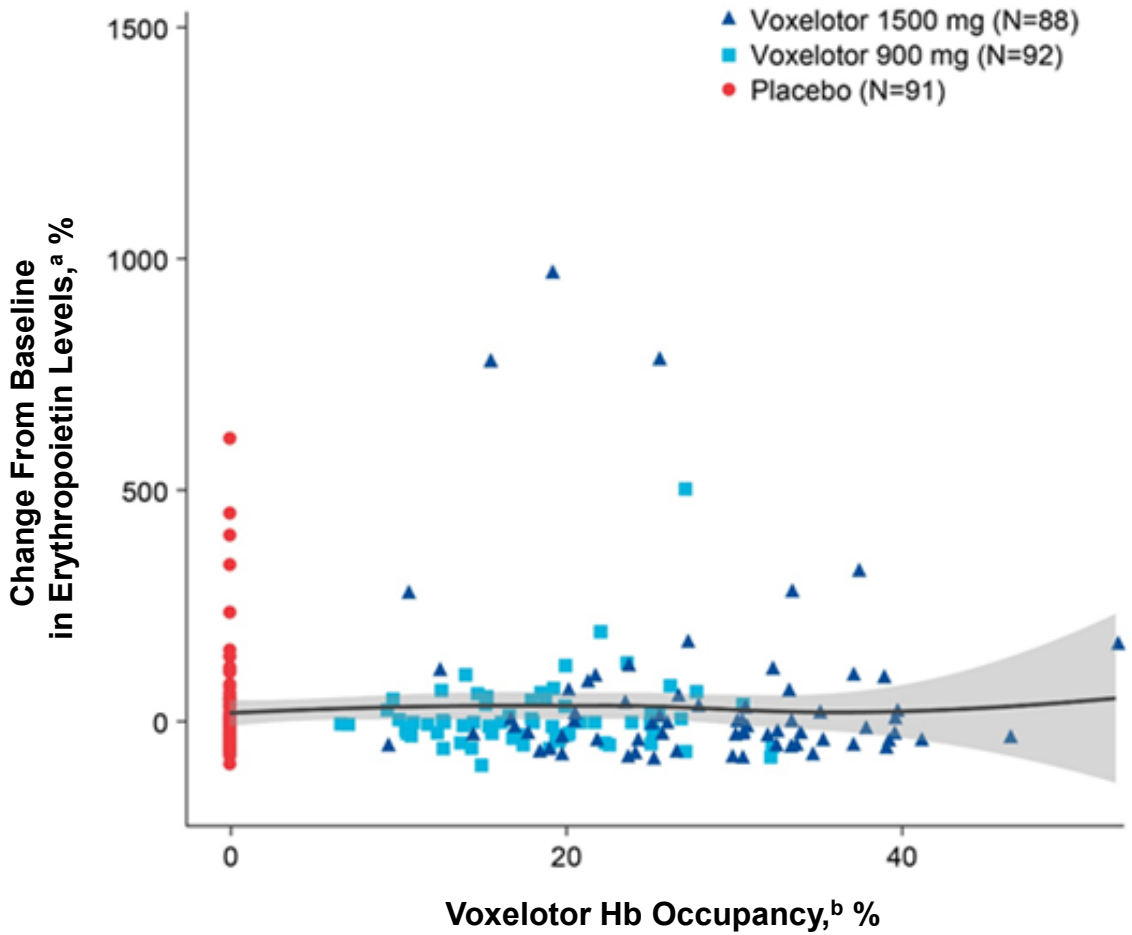
[a]SCD-related adverse events (not shown) include sickle cell anemia with crisis, ACS, pneumonia, priapism, and osteonecrosis. Most grade ≥3 SCD-related TEAEs were sickle cell anemia with crisis.
[b]Excludes SCD-related TEAEs.
[c]Reasons for non-SCD-related treatment discontinuation in patients receiving voxelotor: Abdominal pain (n=2 events), anemia, angina pectoris, nausea, diarrhea, chest pain, pyrexia, hepatitis, hepatocellular injury, hypersensitivity, pulmonary sepsis, type 2 diabetes, and paresthesia (all n=1 event).
[d]Includes both non-SCD-related and SCD-related serious TEAEs.
ACS, acute chest syndrome; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

Common Non-SCD-Related TEAEs (Occurring in ≥10% of Patients)

Preferred Term, n (%)[a]	Voxelotor 1500 mg N=88	Voxelotor 900 mg N=92	Placebo N=91
Patients with ≥1 event	83 (94.3)	86 (93.5)	81 (89.0)
Headache	23 (26.1)	14 (15.2)	20 (22.0)
Diarrhea	18 (20.5)	16 (17.4)	9 (9.9)
Nausea	15 (17.0)	15 (16.3)	9 (9.9)
Arthralgia	13 (14.8)	11 (12.0)	11 (12.1)
Upper respiratory tract infection	12 (13.6)	17 (18.5)	10 (11.0)
Abdominal pain	12 (13.6)	13 (14.1)	7 (7.7)
Fatigue	12 (13.6)	12 (13.0)	9 (9.9)
Rash[b]	12 (13.6)	10 (10.9)	9 (9.9)
Pyrexia	11 (12.5)	10 (10.9)	6 (6.6)
Pain in extremity	10 (11.4)	18 (19.6)	16 (17.6)
Back pain	10 (11.4)	13 (14.1)	10 (11.0)
Vomiting	10 (11.4)	12 (13.0)	11 (12.1)
Pain	8 (9.1)	10 (10.9)	6 (6.6)
Non-cardiac chest pain	7 (8.0)	12 (13.0)	8 (8.8)
Abdominal pain upper	6 (6.8)	11 (12.0)	6 (6.6)

[a]Excludes SCD-related adverse events (sickle cell anemia with crisis, ACS, pneumonia, priapism, and osteonecrosis).
[b]Rash is a grouped term including the following preferred terms: rash, urticaria, rash generalized, rash maculopapular, rash pruritic, rash erythematous, rash vesicular, rash macular, and rash papular.
ACS, acute chest syndrome; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

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



[a]Change in erythropoietin from baseline at week 24 was calculated using the last observation carried forward.
[b]Voxelotor Hb occupancy was calculated based on steady-state trough exposures.
Hb, hemoglobin.

Conclusions

- Treatment with voxelotor achieved rapid, robust, and sustained improvement in Hb and hemolysis
- Voxelotor 1500 mg dose demonstrated:
  - Hb increase of >1 g/dL in 59.5% of patients
  - Anemia improvement irrespective of baseline anemia severity or hydroxyurea use
- Voxelotor was safe and well tolerated
- Fewer VOCs were observed, with a substantial increase in Hb
- 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

Hb, hemoglobin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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