Higher Hemoglobin Levels Achieved with Voxelotor Are Associated with Lower Vaso-Occlusive Crisis Incidence: 72-Week Analysis from the HOPE Study

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Disclosures

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- Research funding: Agios, Pfizer

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Background

SCD is a lifelong, inherited disorder characterized by sickle hemoglobin polymerization that results in red blood cell sickling and in complications such as hemolytic anemia, VOCs, endothelial dysfunction, and organ damage[1]

Large and rapid increases in hemoglobin concentration in response to red blood cell transfusions have raised concerns of hyperviscosity and the associated increased risk of vaso-occlusive complications[2,3]

- Current transfusion guidelines recommend raising Hb to no higher than 10 g/dL in adults[2]

Voxelotor is an oral, once-daily sickle hemoglobin–polymerization inhibitor indicated for treatment of SCD in adults and adolescents aged ≥12 years[4]

Here we report a post hoc analysis assessing the association between average on-treatment Hb and VOC incidence over 72 weeks.

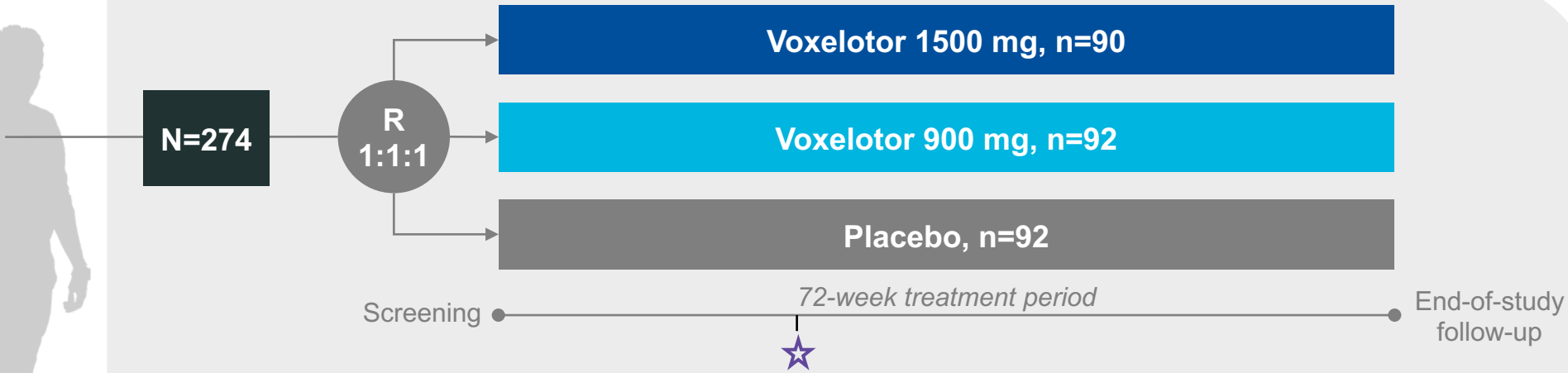
Hb, hemoglobin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Kato GJ, et al. *Nat Rev Dis Primers.* 2018;4:18010. 2. DeBaun M, et al. *Blood Adv.* 2020;4(8):1554-1588. 3. Swerdlow PS. *Hematology Am Soc Hematol Educ Program.* 2006;48-53.
4. Oxbryta. Prescribing information. Global Blood Therapeutics, Inc; 2019.

HOPE Trial: Study Design[1,2]

Phase 3, randomized, double-blind, placebo-controlled, multicenter trial evaluating the efficacy and safety of voxelotor

- Aged 12 to 65 years with confirmed SCD[a]
- Hb 5.5 to 10.5 g/dL
- Between 1 and 10 VOCs in prior 12 months
- Concomitant HU, if stable for ≥3 months



Primary efficacy endpoint

- **Hb response rate:** percentage of participants with Hb increase **>1.0 g/dL** at 24 weeks

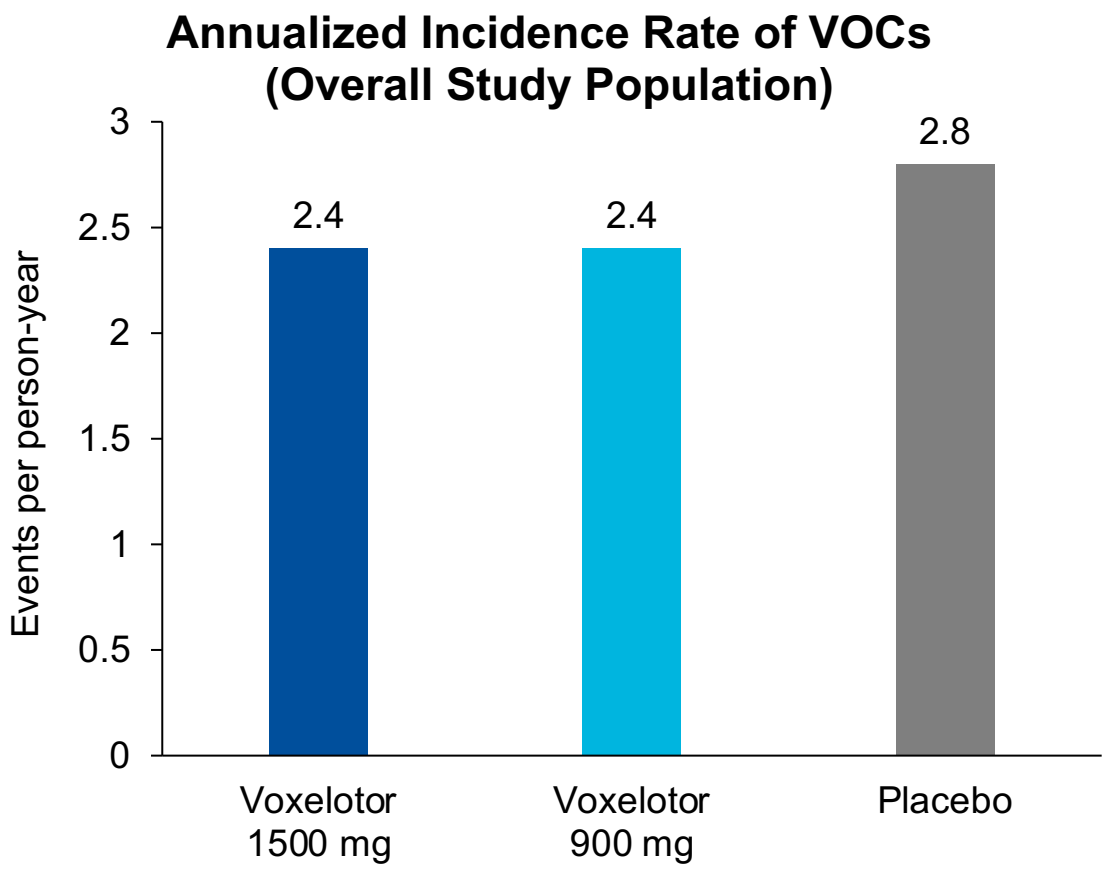
Key secondary efficacy endpoints

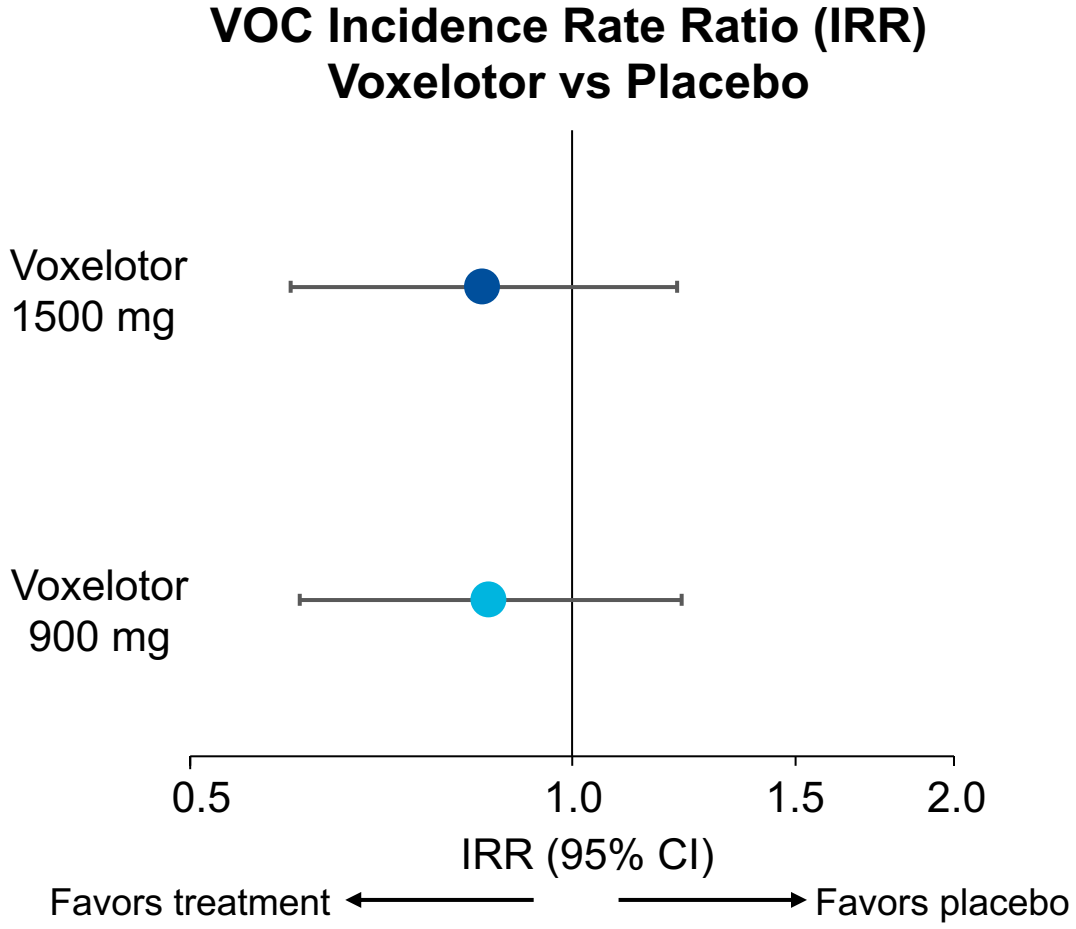
- **Hemolysis markers:** change from baseline to week 24
- **Hb level:** change from baseline to week 24
- **Annualized incidence of VOCs:** final analysis at 72 weeks

[a]Eligible genotypes: HbSS, HbSβ^0, HBSβ$^+$, HbSC, and other documented variants.
Hb, hemoglobin; HbSβ^0, sickle beta zero thalassemia; HbSβ$^+$, sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; R, randomization; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Vichinsky E, et al. *N Engl J Med*. 2019;381(6):509-519. 2. Data on file. GBT, South San Francisco, CA.

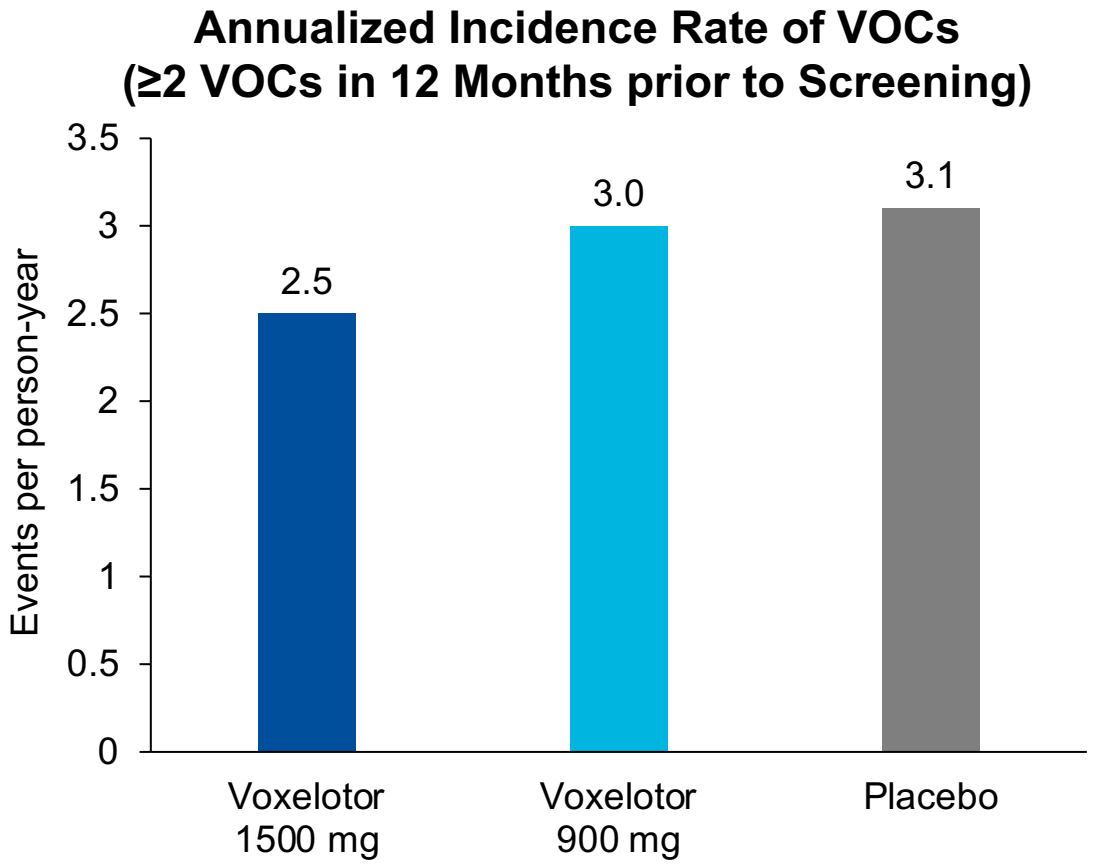
VOC Annualized Incidence Rates Were Numerically Lower with Voxelotor

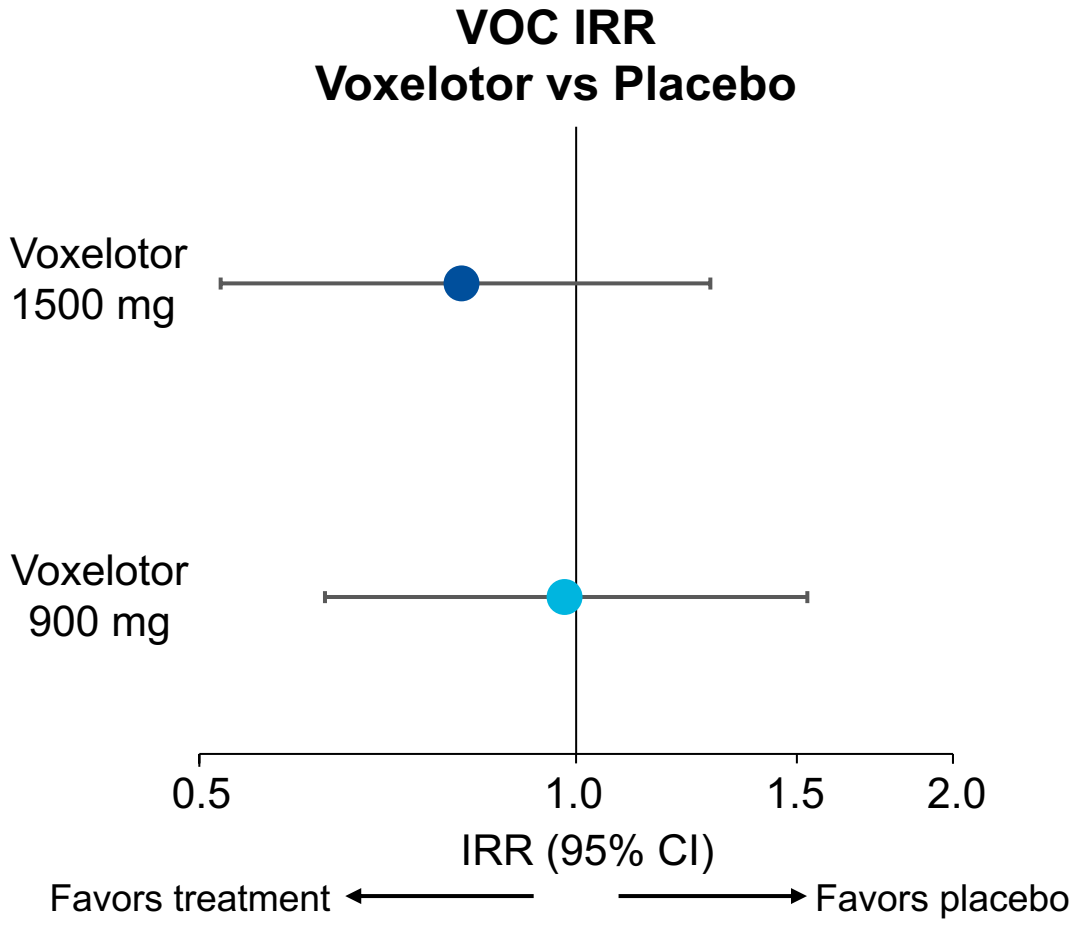




VOC, vaso-occlusive crisis.

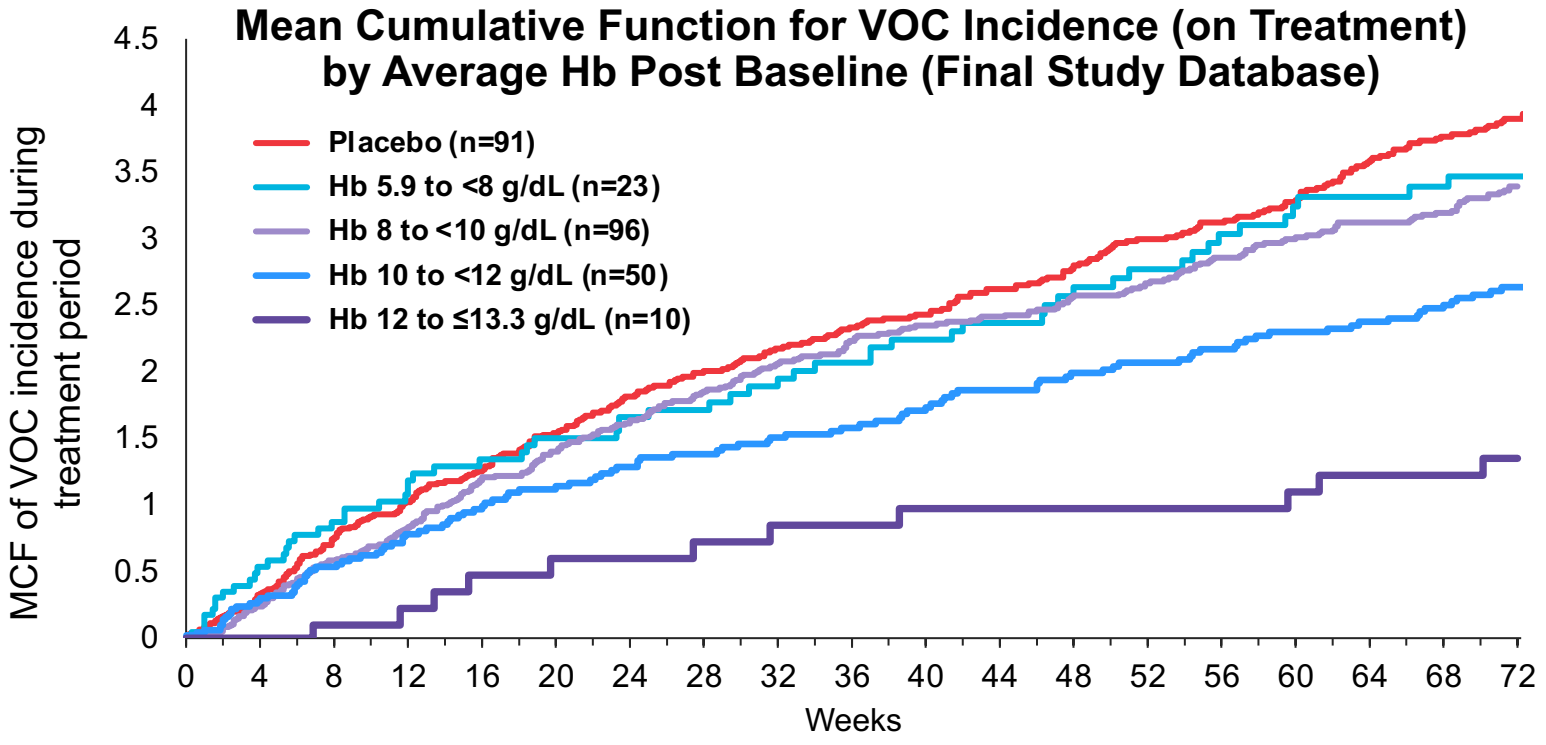
VOC Annualized Incidence Rates Were Numerically Lower with Voxelotor in Patients with ≥2 VOCs 12 Months prior to Screening





IRR, incidence rate ratio; VOC, vaso-occlusive crisis.

Incidence Rate of VOCs Was Lowest in Patients Achieving the Highest Hemoglobin Levels



No. at risk	Hb Average	Wk	0	4	8	12	16	20	24	36	48	60	72
Placebo	All		91	90	87	83	82	79	75	70	66	64	40
Voxelotor Pooled	Hb 5.9 to <8 g/dL		23	21	20	19	19	19	19	17	15	14	6
	Hb 8 to <10 g/dL		96	96	94	92	90	88	84	78	76	72	55
	Hb 10 to <12 g/dL		50	50	46	43	42	41	41	40	39	39	30
	Hb 12 to ≤13.3 g/dL		10	10	9	8	8	8	8	8	8	8	6

Baseline demographics were generally well balanced across Hb strata

Summary excludes VOC events after treatment discontinuation and events after HU initiation post randomization for patients with no HU use at baseline. Summary excludes patients without post-baseline Hb lab assessment. Hb values are as observed based on assessments collected through the end of the week 72 visit window. Hb values collected after treatment discontinuation (for patients with last dose prior to the week 72 visit window), after withdrawal of consent, after study discontinuation, and after HU initiation post randomization for patients with no HU use at baseline were excluded.
Hb, hemoglobin; HU, hydroxyurea; MCF, mean cumulative function; VOC, vaso-occlusive crisis; wk, week.

Conclusions

Treatment with once-daily voxelotor resulted in increases in average Hb concentrations that reached or exceeded 10 g/dL in a substantial number of study participants.

In contrast with the theoretical concern of higher VOC risk with higher Hb levels, patients who had the highest average Hb levels over 72 weeks with voxelotor experienced the fewest VOCs, with a stepwise reduction in VOC rate with each increase in Hb stratum.

These results suggest the mechanism of reducing hemolysis and raising Hb in individuals with SCD, such as via inhibition of polymerization, is important.

The improvement in red blood cell health, including increased deformability and decreased viscosity, suggest higher Hb thresholds could be considered in patients on voxelotor.

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

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