Concomitant Hydroxyurea and Voxelotor: Results From the HOPE Study

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BACKGROUND

- Voxelotor is a first-in-class sickle hemoglobin (HbS) polymerization inhibitor being developed for the treatment of sickle cell disease (SCD). In the phase 3 HOPE trial, treatment with voxelotor 1500 mg and 900 mg daily demonstrated rapid and sustained improvements in hemoglobin (Hb) levels and markers of hemolysis compared with placebo.[1,2]
- Hydroxyurea induces fetal hemoglobin (HbF) and is approved by both the US Food and Drug Administration and the European Medicines Agency as a treatment for SCD.[3-5]
- Because both voxelotor and hydroxyurea can affect anemia and hemolysis, and potentially have additive mechanisms of protection against HbS polymerization,[1,4] the effects of concomitant hydroxyurea in the setting of voxelotor treatment were investigated.

OBJECTIVES

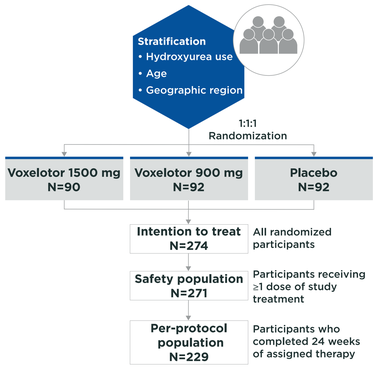
- To examine the safety of concomitant hydroxyurea and voxelotor use and the effect on laboratory parameters associated with hydroxyurea in participants from the phase 3 HOPE study.

METHODS

Study Design

- The HOPE study was a phase 3, randomized, placebo-controlled, double-blind, multicenter study comparing the efficacy and safety of voxelotor (1500 mg and 900 mg daily) versus placebo in participants with SCD aged 12 to 65 years (**Figure 1**).
- A post hoc analysis was performed using available data for all participants at the interim data cutoff on October 31, 2018.
- Changes in laboratory parameters and markers for hydroxyurea adherence, including Hb, percentage of HbF, mean corpuscular volume (MCV), absolute neutrophil count (ANC), and absolute reticulocyte count (ARC), were compared in participants with or without concomitant hydroxyurea use through week 24 of the study period.
- Safety was assessed via treatment-emergent adverse event (TEAE) reporting in addition to the above laboratory parameters.

Figure 1. HOPE Study Design



ANC, absolute neutrophil count; ARC, absolute reticulocyte count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSC, hemoglobin SC disease; HbSS, sickle cell anemia; HbSβ, sickle beta thalassemia; MCV, mean corpuscular volume; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

RESULTS

Baseline Characteristics

- A total of 179 of 274 (65%) participants were receiving hydroxyurea (**Table 1A**) and 95 of 274 (35%) participants were not receiving hydroxyurea (**Table 1B**) at study enrollment. Both groups were evenly distributed across the 3 treatment arms and evaluated for specific laboratory parameters including Hb, percentage of HbF, MCV, ANC, and ARC.

Table 1. Demographics and Baseline Characteristics
A. Participants With Concomitant Hydroxyurea Use

	Voxelotor 1500 mg (n=58)	Voxelotor 900 mg (n=63)	Placebo (n=58)
Age, median (range), years	22 (12-59)	22 (12-59)	26 (12-52)
12 to <18 years, n (%)	12 (21)	13 (21)	13 (22)
≥18 years, n (%)	46 (79)	50 (79)	45 (78)
Hb level, mean (SD), g/dL	8.8 (1.1)	8.5 (1.0)	8.7 (1.2)
HbF, mean (SD), %	11.1 (6.8)	11.9 (7.6)	12.2 (12.9)
MCV, mean (SD), fL	100.2 (16.0)	100.9 (17.8)	99.5 (14.1)
ANC, mean (SD), $x10^9$/L	4.1 (1.9)	5.2 (2.6)	4.6 (2.1)
ARC, mean (SD), $x10^9$/L	268.6 (115.7)	292.8 (145.0)	281.7 (134.3)
Hydroxyurea, mean (SD), mg/kg/day	20.5 (10.0)	17.6 (7.1)	18.9 (9.4)

B. Participants Without Concomitant Hydroxyurea Use

	Voxelotor 1500 mg (n=32)	Voxelotor 900 mg (n=29)	Placebo (n=34)
Age, median (range), years	27 (12-54)	28 (13-52)	28 (12-64)
12 to <18 years, n (%)	2 (6)	2 (7)	4 (12)
≥18 years, n (%)	30 (94)	27 (93)	30 (88)
Hb level, mean (SD), g/dL	8.4 (1.0)	7.9 (1.1)	8.5 (0.8)
HbF, mean (SD), %	6.5 (3.9)	6.1 (5.7)	7.5 (5.7)
MCV, mean (SD), fL	87.8 (10.1)	91.8 (10.5)	91.0 (9.5)
ANC, mean (SD), $x10^9$/L	5.5 (1.9)	5.3 (1.8)	4.9 (1.4)
ARC, mean (SD), $x10^9$/L	354.1 (119.5)	376.1 (107.9)	374.1 (99.0)

ANC, absolute neutrophil count; ARC, absolute reticulocyte count; Hb, hemoglobin; HbF, fetal hemoglobin; MCV, mean corpuscular volume; SD, standard deviation.

- Baseline laboratory values documented the effects of current hydroxyurea treatment, with higher average Hb, MCV, and percentage of HbF, but slightly lower average ANC compared with those not receiving hydroxyurea.

Voxelotor-Associated Hb Improvements Were Similar Regardless of Baseline Hydroxyurea Use

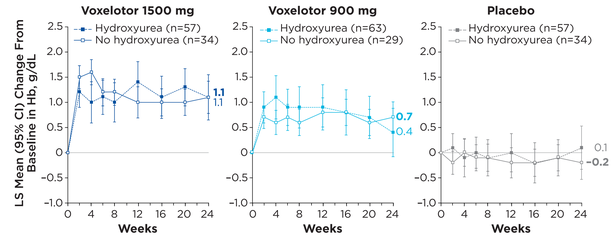
- Voxelotor treatment led to significant dose-dependent Hb increases, regardless of concomitant hydroxyurea, and Hb remained relatively stable over time (**Table 2**, **Figure 2**).
- A lower average ARC was noted, which was attributed to the increased Hb level.

Table 2. Mean Change From Baseline to Week 24 (95% CI[a]) in Laboratory Parameters by Hydroxyurea Use

	Voxelotor 1500 mg		Voxelotor 900 mg		Placebo	
	Hydroxyurea	No hydroxyurea	Hydroxyurea	No hydroxyurea	Hydroxyurea	No hydroxyurea
Hb, g/dL (n=229)	1.3 (1.0, 1.6)	1.3 (0.8, 1.8)	0.7 (0.5, 1.0)	0.8 (0.3, 1.3)	0.0 (−0.2, 0.2)	0.0 (−0.2, 0.3)
HbF, % (n=131)	−1.8 (−3.1, −0.5)	0.2 (−0.9, 1.3)	−1.8 (−3.7, 0.1)	−0.7 (−1.1, −0.3)	−0.1 (−1.8, 1.5)	0.5 (0.0, 1.1)
MCV, fL (n=211)	−3.2 (−6.1, −0.3)	−1.3 (−3.6, 1.0)	−0.7 (−2.9, 1.4)	−1.2 (−3.7, 1.3)	0.8 (−1.0, 2.5)	0.3 (−1.4, 2.0)
ANC, $x10^9$/L (n=229)	0.0 (−0.5, 0.4)	−0.4 (−1.2, 0.3)	−0.1 (−0.8, 0.6)	0.1 (−0.6, 0.7)	−0.3 (−0.7, 0.2)	0.4 (−0.4, 1.2)
ARC, $x10^9$/L (n=229)	−43.4 (−75.0, −11.9)	−28.6 (−72.9, 15.8)	−11.2 (−34.9, 12.6)	−4.8 (−41.5, 31.9)	3.0 (−23.1, 29.2)	0.1 (−49.0, 49.1)

[a]CI not adjusted for multiplicity.
ANC, absolute neutrophil count; ARC, absolute reticulocyte count; CI, confidence interval; Hb, hemoglobin; HbF, fetal hemoglobin; MCV, mean corpuscular volume.

Figure 2. Mean Change in Hb From Baseline to Week 24 by Hydroxyurea Use

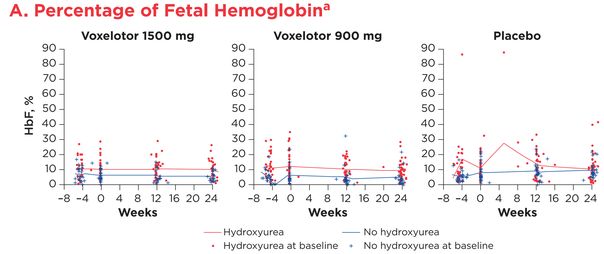


Error bars represent 95% CI. Results presented are estimated from a MMRM adjusting for baseline Hb value within each hydroxyurea subgroup. n represents the number of individuals who contributed any observations to the model. The sample sizes vary over time points. Laboratory values within 8 weeks after any red blood cell transfusion were imputed by the last value prior to the transfusion.
CI, confidence interval; Hb, hemoglobin; LS, least squares; MMRM, mixed model for repeated measures.

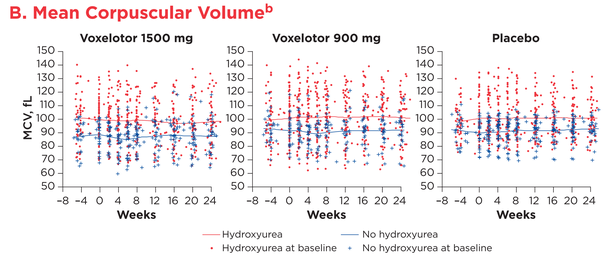
Voxelotor Treatment Was Not Associated With Changes in Hydroxyurea Adherence Parameters

- Observed adherence parameters, including average percentage of HbF, MCV, and ANC, were unchanged during the treatment period, demonstrating stable hydroxyurea exposure (**Figure 3**).

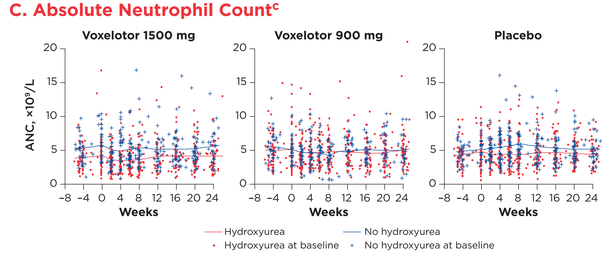
Figure 3. HbF Percentage, MCV, and ANC Remained Stable Throughout 24 Weeks With Voxelotor
A. Percentage of Fetal Hemoglobin[a]



B. Mean Corpuscular Volume[b]



C. Absolute Neutrophil Count[c]



[a]The smooth line for each subgroup was estimated from a local regression with a smoothing parameter of 0.45.
[b]The smooth line for each subgroup was estimated from a local regression with a smoothing parameter of 0.35.
[c]The smooth line for each subgroup was estimated from a local regression with a smoothing parameter of 0.35.
ANC, absolute neutrophil count; HbF, fetal hemoglobin; MCV, mean corpuscular volume.

- Overall, similar percentages of participants reported any TEAE among participants treated with hydroxyurea (voxelotor 1500 mg, 98.2%; voxelotor 900 mg, 98.4%; placebo, 96.5%) and without hydroxyurea (voxelotor 1500 mg, 93.5%; voxelotor 900 mg, 96.6%; placebo, 97.1%).
- Percentages of participants reporting any serious TEAE were also similar among participants treated with hydroxyurea (voxelotor 1500 mg, 52.6%; voxelotor 900 mg, 54.0%; placebo, 49.1%) and without hydroxyurea (voxelotor 1500 mg, 45.2%; voxelotor 900 mg, 44.8%; placebo, 52.9%).

CONCLUSIONS

- In the HOPE study, participants treated with voxelotor had increased Hb levels compared with placebo, irrespective of hydroxyurea use.
- Significant voxelotor-associated Hb increases were observed for participants on concomitant hydroxyurea and were equivalent to those observed in participants not taking hydroxyurea.
- The lack of observed changes in percentage of HbF, MCV, and ANC was consistent with stable hydroxyurea exposure throughout the treatment period, thus addressing questions regarding hydroxyurea compliance during the study.
- Comparable TEAE rates were observed across study arms and between participants with or without hydroxyurea use.
- The additive treatment effects on anemia and hemolysis by voxelotor, as well as the comparable TEAE rates observed across study arms, suggest that combination therapy with hydroxyurea may be safe and effective for optimal disease modification.

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