Baseline Patient Characteristics From a UK Early Access to Medicines Scheme (EAMS) With Voxelotor, a HbS Polymerization Inhibitor, for the Treatment of Hemolytic Anemia Due to Sickle Cell Disease

Perla Eleftheriou, MD, MRCP, FRCP[1]; Joseph Sharif, MRCP, FRCP[2]; Rachel Kesse-Adu, MBBS, FRCP[3]; Miriam Filian-Gloor[4]; Arvind Agrawal[4]; Giovanna Barcelos, MS[4]; Paul Telfer, MD, FRCP[5]

[1]University College Hospital London, London, UK; [2]Manchester University NHS Foundation Trust, Manchester, UK; [3]Guy's and St Thomas' Hospital, London, UK; [4]Global Blood Therapeutics, South San Francisco, CA, USA; [5]Queen Mary University of London, London, UK

INTRODUCTION

- Sickle cell disease (SCD) is one of the most common genetic disorders in the United Kingdom, with an estimated 1 in 4600 people living with SCD and affecting 1 in 2517 live births in England.[1,2]
- SCD pathophysiology is driven by the polymerization of sickle hemoglobin (HbS), which causes red blood cell sickling that leads to chronic hemolytic anemia, painful vaso-occlusive crises (VOCs), and end-organ damage.[3]
- The standard of care for SCD typically includes blood transfusions and treatment with hydroxyurea (HU).[3]
- Voxelotor is a first-in-class HbS polymerization inhibitor approved in the United States for the treatment of SCD in patients aged ≥4 years, and in the European Union, Great Britain, United Arab Emirates, Oman, and Kuwait for patients aged ≥12 years.[4-6]
- Voxelotor has been provided to eligible patients with SCD in the United Kingdom through a Medicines and Healthcare Products Regulatory Agency (MHRA)-approved Early Access Medicines Scheme (EAMS) and the Named Patient Program (NPP).[5,7]
- Both EAMS and NPP allow patients to receive new, unlicensed medicines when there is a clear unmet need.[7]

OBJECTIVE

- To describe the UK patient population participating in the voxelotor EAMS and NPP for the treatment of hemolytic anemia due to SCD and report on changes in hemoglobin (Hb), hemolytic markers, and safety data from the treatment period.

METHODS

- Patients with hemolytic anemia due to SCD aged ≥12 years with Hb ≤10.5 g/dL received voxelotor via either the EAMS or the NPP.
  - The EAMS permitted patients to receive voxelotor as a monotherapy or in combination with HU, provided the HU dosage was stable for 3 months before initiating voxelotor.
  - The NPP allowed patients who were ineligible for or intolerant of HU, were unresponsive to HU, or had stopped taking HU to receive voxelotor.
- Patients who received voxelotor through the NPP were switched to EAMS-labeled voxelotor after the approval of the EAMS by the MHRA; thus, all patients are currently receiving EAMS-labeled voxelotor.
- The information collected from patients included demographics, comorbidities, concomitant treatments (including transfusions), medically confirmed adverse events, Hb and hemolytic markers, crises requiring treatment or hospitalization, and therapy discontinuation.
- All safety data were validated, assessed for causality, and reported to the appropriate healthcare authorities; adverse events of interest included rash, diarrhea, headache, and those that led to voxelotor dose modification or discontinuation.

RESULTS

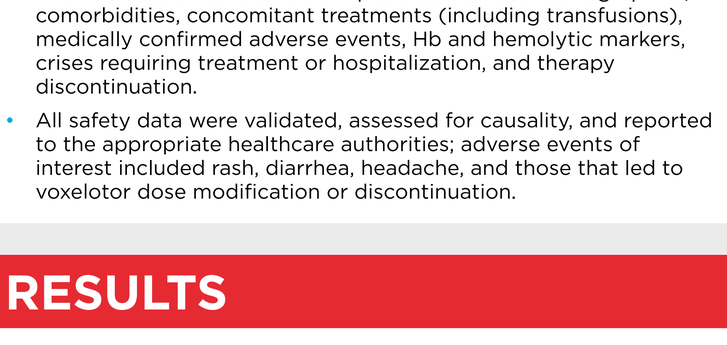
Patients

- As of August 22, 2022, 90 patients were enrolled (n=61, EAMS; n=29, NPP).
- Patients had a mean (SD) age of 37.82 (15.01) years, ranging 12 to 66 years; 53.33% were female, 75.56% were of African or African Caribbean descent, and 97.78% had the HbSS (homozygous for SCD) genotype (**Table 1**).
- At baseline, 28 patients (45.90%) were taking HU, and 11 (18.03%) had discontinued previous use of HU.
- The mean (SD) duration of voxelotor treatment was 14.44 (13.05) weeks (n=52), with the range of treatment being 0.14 to 50.14 weeks.

Hb Levels

- In 46 patients for whom Hb measurements were available, mean (SD) peak Hb increased from baseline by 1.1 (1.38) g/dL (**Figure 1**); the mean (SD) duration of voxelotor treatment for those 46 patients was 15.94 (13.15) weeks, with the range of treatment being 2.43 to 50.14 weeks.

Figure 1. Mean Peak CFB in Hb Among Voxelotor-Treated Patients



Peak Hb was defined as the highest post-baseline Hb value while on voxelotor treatment.
CFB, change from baseline; Hb, hemoglobin.

Table 1. Patient Demographics and Baseline Characteristics

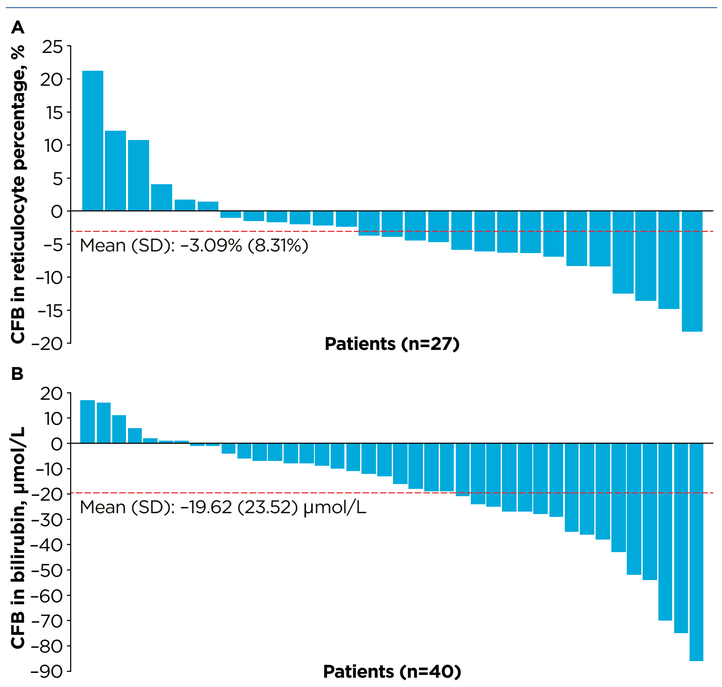
	Total (N=90)	EAMS (n=61)	NPP (n=29)
Age, years			
Mean (SD)	37.82 (15.01)	37.34 (15.46)	38.83 (14.24)
Range	12-66	12-65	16-66
Female, n (%)	48 (53.33)	33 (54.10)	15 (51.72)
Ethnicity, n (%)			
African	13 (14.44)	9 (14.75)	4 (13.79)
African Caribbean	55 (61.11)	48 (78.69)	7 (24.14)
Genotype, n (%)			
HbSS	88 (97.78)	59 (96.72)	29 (100)
Other	2 (2.22)	2 (3.28)	0 (0)
Hb, g/dL			
Mean (SD)	7.54 (1.43)	7.61 (1.40)	7.4 (1.49)
Range	4.6-10.8	4.9-10.8	4.6-10.1
Absolute reticulocytes, ×10⁹/L			
Mean (SD)	262.84 (145.01)	266.42 (148.57)	255.05 (139.24)
Range	24.9-690.3	24.9-690.3	37-533
Reticulocyte percentage, %			
Mean (SD)	12.1 (6.55)	11.79 (6.40)	12.97 (7.10)
Range	1.24-31.8	1.24-31.8	3-26.1
Missing values, n (%)	29 (32.22)	16 (26.23)	13 (44.83)
Total bilirubin, µmol/L			
Mean (SD)	58.09 (40.03)	60.27 (40.29)	53.50 (39.8)
Range	7-228	13-228	7-174
Missing values, n (%)	3 (3.33)	2 (3.28)	1 (3.45)
Indirect bilirubin, µmol/L			
Mean (SD)	40.95 (31.7)	44.52 (34.84)	29.44 (14.31)
Range	5-135	5-135	8-45
Missing values, n (%)	52 (57.78)	32 (52.46)	20 (68.97)
LDH,[a] IU/L			
Mean (SD)	589.63 (248.54)	589.63 (248.54)	
Range	225-1434	225-1434	—
Missing values, n (%)	20 (32.79)	20 (32.79)	—
On HU,[a] n (%)	28 (45.9)	28 (45.9)	—
Previously on HU,[a] n (%)	11 (18.03)	11 (18.03)	—
On crizanlizumab,[a] n (%)	1 (1.64)	1 (1.64)	—
Alloimmunization,[a] n (%)	12 (19.67)	12 (19.67)	—
VOC requiring hospitalization in previous 12 months[a]			
Mean (SD)	0.84 (1.52)	0.84 (1.52)	—
Range	0-8	0-8	
Hospitalizations 12 months before voxelotor initiation,[a] n (%)			
VOC	15 (24.59)	15 (24.59)	
ACS	3 (4.92)	3 (4.92)	
Transfusion	6 (9.84)	6 (9.84)	—
Hyperhemolysis	2 (3.28)	2 (3.28)	
Other	6 (9.84)	6 (9.84)	
None	29 (47.54)	29 (47.54)	
≥3 ED admissions in previous 12 months[a]			
n (%)	6 (9.84)	6 (9.84)	—

[a]n=61. A "—" symbol indicates that data were not captured in patient charts.
ACS, acute chest syndrome; EAMS, Early Access to Medicines Scheme; ED, emergency department; Hb, hemoglobin; HbSS, homozygous for SCD; HU, hydroxyurea; LDH, lactate dehydrogenase; NPP, Named Patient Program; VOC, vaso-occlusive crisis.

Hemolytic Markers

- Treatment with voxelotor improved markers of hemolysis.
- The mean (SD) peak change from baseline in reticulocyte percentage was −3.09% (8.31%) (n=27) (**Figure 2A**); the mean (SD) duration of treatment for those 27 patients was 15.31 (11.93) weeks, range: 2.43 to 45.00 weeks.
- The mean (SD) peak change from baseline in absolute reticulocyte count was −54.34 (158.87) × 10^9/L (n=44); the mean (SD) duration of treatment for those 44 patients was 15.34 (12.33) weeks, range: 2.43 to 47.29 weeks.
- The mean (SD) peak change from baseline in total bilirubin was −19.62 (23.52) µmol/L (n=40) (**Figure 2B**); the mean (SD) duration of treatment for those 40 patients was 14.58 (12.00) weeks, range: 2.43 to 47.29 weeks.

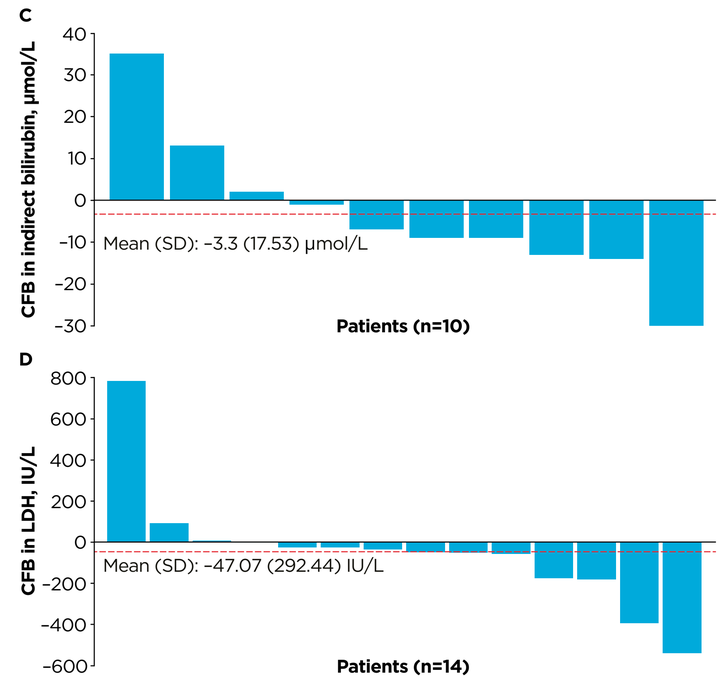
Figure 2. (A) Mean Peak CFB in Reticulocyte Percentage and (B) Mean Peak CFB in Total Bilirubin



Peak reticulocyte percentage and peak total bilirubin are defined as the lowest post-baseline values while on voxelotor treatment.
CFB, change from baseline.

- The mean (SD) peak change from baseline in indirect bilirubin was −3.3 (17.53) µmol/L (n=10) (**Figure 2C**); the mean (SD) duration of treatment for those 10 patients was 15.70 (10.73) weeks, range: 5.00 to 39.43 weeks.
- The mean (SD) peak change from baseline in lactate dehydrogenase (LDH) was −47.07 (292.44) IU/L (n=14) (**Figure 2D**); the mean (SD) duration of treatment for those 14 patients was 9.05 (4.85) weeks, range: 2.71 to 18.00 weeks.

Figure 2. (C) Mean Peak CFB in Indirect Bilirubin and (D) Mean Peak CFB in LDH



Peak indirect bilirubin and peak LDH are defined as the lowest post-baseline values while on voxelotor treatment.
CFB, change from baseline; LDH, lactate dehydrogenase.

Safety

- Of the 61 patients in the EAMS population, 8 (13.11%) experienced an adverse event (**Table 2**).
- Diarrhea, nausea, and rash occurred in 2 (3.28%) patients each; other adverse events were reported in 2 patients.

Table 2. Adverse Events in EAMS Patients Treated With Voxelotor

	Patients (n=61)
Patients with adverse events, n (%)	8 (13.11)
Reported adverse events, n (%)	
Diarrhea	2 (3.28)
Nausea	2 (3.28)
Rash	2 (3.28)
Other	2 (3.28)

EAMS, Early Access to Medicines Scheme.

LIMITATIONS

- Limitations of this study include the reliance on data from patient medical records and the input of that data from each site, small sample sizes, and variability in voxelotor treatment duration and adherence.
- Measurements of hematologic markers were not mandated but were collected as part of routine clinical care; thus, there was inconsistency in the measurement of certain hemolytic markers.
- Unlike a clinical trial, adverse events were recorded spontaneously and not at particular points in time.

CONCLUSIONS

- The UK EAMS and NPP provide voxelotor to patients with SCD with limited treatment options.
- The EAMS patient population is representative of a typical UK patient with SCD and hemolytic anemia.
- The demographic and baseline data provided here show the characteristics of patients selected for the early access scheme and highlight the unmet treatment needs among patients with SCD in the United Kingdom.
- Laboratory measures, such as Hb and hemolytic markers, are critical in defining patient eligibility, monitoring efficacy, and providing comparisons to follow-up measures in patients receiving voxelotor.
- Preliminary analyses are commensurate with both clinical study data and other retrospective analyses in that treatment with voxelotor improved Hb levels and reduced markers of hemolysis (reticulocyte count, LDH, and total and indirect bilirubin).
- The adverse events reported in the EAMS are consistent with those reported in clinical trials.
- Further analyses on the impact of voxelotor on clinical outcomes among the patients participating in the EAMS and NPP are ongoing.

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DISCLOSURES

- **Perla Eleftheriou:** advisory boards: Novartis, Forma Therapeutics, Alexion, Global Blood Therapeutics; principal investigator in clinical trials: Global Blood Therapeutics; sponsored educational meetings: Global Blood Therapeutics, Novartis. **Joseph Sharif:** advisory boards: Novartis, Global Blood Therapeutics, Forma Therapeutics. **Rachel Kesse-Adu:** honorarium: Global Blood Therapeutics; medical education advisory boards: Novartis, Vertex. **Miriam Filian-Gloor:** employee, equity ownership: Global Blood Therapeutics. **Arvind Agrawal:** employee, equity ownership: Global Blood Therapeutics. **Giovanna Barcelos:** employee: Global Blood Therapeutics **Paul Telfer:** research funding: Bluebird Bio; honoraria: Global Blood Therapeutics, Terumo, Bluebird Bio; membership: Global Blood Therapeutics, Pfizer, ApoPharma.
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