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ORIGINAL PAPER

Haemoglobinopathies

Baseline characteristics of Ghanaian children and adults enrolled in PIVOT, a randomised clinical trial of hydroxyurea in HbSC disease in sub-Saharan Africa

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Summary

HbSC disease is a common form of sickle cell disease with significant morbidity and early mortality. Whether hydroxyurea is beneficial for HbSC disease is unknown. Prospective Identification of Variables as Outcomes for Treatment (PIVOT, Trial ID PACTR202108893981080) is a double-blind, randomised, placebo-controlled phase II trial of hydroxyurea for people with HbSC, age 5–50 years, in Ghana. After screening, participants were randomised to placebo (standard of care) or hydroxyurea. The primary outcome is the cumulative incidence of haematological toxicities during 12 months of blinded treatment; secondary outcomes include multiple laboratory and clinical assessments. Between April 2022 and June 2023, 112 children and 102 adults were randomised, including 44% females and average age 21.6 ± 14.5 years. Participants had substantial morbidity including previous hospitalisations (93%), vaso-occlusive events (86%), malaria (79%), often received transfusions (20%), with baseline haemoglobin 11.0 ± 1.2 g/dL and foetal haemoglobin 1.8% ± 1.5%. The spleen was palpable in six children and one adult, and ultrasonographic volumes were collected. Proliferative sickle retinopathy was common (30% children, 75% adults), but

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proteinuria was less common (3% children, 8% adults). Whole blood viscosity, ektacytometry, point-of-sickling, transcranial Doppler, near-infrared spectrometry (NIRS), 6-minute walk, and quality of life were also measured. Now fully enrolled, PIVOT will document the safety and potential benefits of hydroxyurea on clinical and laboratory outcomes in HbSC disease.

KEYWORDS
adults, children, HbSC disease, hydroxyurea, study endpoints, sub-Saharan Africa

INTRODUCTION

Sickle cell disease (SCD) is a common inherited haemoglobinopathy with substantial morbidity and early mortality.[1] The highest burden of SCD is within sub-Saharan Africa, where over 400 000 affected babies are born each year.[2] The most common form of SCD is homozygous HbSS disease, with two mutated alleles of the beta-globin gene (*HBB*) that result in the production of HbS. The second most common form, haemoglobin SC (HbSC) disease, is a compound heterozygous condition with one HbS mutation and one HbC mutation.[3] In the United States, HbSC disease accounts for ~30% of SCD,[4,5] but since HbC originated in West Africa,[6] HbSC disease is more common in that region and comprises ~50% of SCD cases identified by newborn screening in Ghana.[7]

Individuals with all SCD genotypes are at risk for developing acute and chronic clinical complications including haemolytic anaemia, recurrent vaso-occlusive painful episodes, and progressive organ damage. Natural history studies from the US-based Cooperative Study of Sickle Cell Disease (CSSCD) and the Jamaican Cohort Study several decades ago documented that as a group, people with HbSC have a longer life expectancy than those with HbSS, and children with HbSC have an overall milder clinical course than HbSS, but some develop severe and life-threatening complications at a young age and experience significant morbidity and early mortality.[8–15] Certain complications like avascular necrosis (AVN, osteonecrosis) of the femoral heads and proliferative retinopathy are at least as common in HbSC as HbSS, if not higher, possibly due to higher haemoglobin concentration and hyperviscosity.[16–18] A recent retrospective study documented that many adults with HbSC disease meet the criteria for severe disease (≥3 sickle-associated moderate-to-severe pain episodes per year, history of acute chest syndrome, and/or severe symptomatic anaemia interfering with daily activities or quality of life),[19] and a US multicentre cross-sectional report similarly confirms significant complications,[18] but a contemporary detailed description of the natural history of HbSC disease and its complications, especially in adulthood, is lacking.

From a management and treatment perspective, HbSC has received much less attention with regard to research and clinical practice compared with HbSS, and optimal management strategies are unclear. For example, the 2014 National Heart Lung and Blood Institute evidence-based management guidelines for SCD recommended hydroxyurea for adults and children with HbSS, beginning as young as age 9 months.[20] In contrast, there were no hydroxyurea recommendations for HbSC, and consequently, the treatment of HbSC was recognised as a key knowledge gap.[21] Published evidence has been mostly retrospective or observational, but some benefits of hydroxyurea treatment for HbSC have been reported.[22–24] There is a pressing need for rigorous, prospective data to evaluate the efficacy and safety of hydroxyurea in HbSC disease, particularly in African populations where the disease burden is highest.

To address this knowledge gap, we designed PIVOT (Prospective Identification of Variables as Outcomes for Treatment), a phase II double-blind randomised placebo-controlled trial to test the primary hypothesis that hydroxyurea in children and adults with HbSC disease is safe and will not result in excess haematological toxicities. Amongst several key secondary objectives is the evaluation of multiple sickle-related clinical, laboratory, and exploratory measurements to determine the benefits of treatment and to identify suitable end-points for a future definitive phase III trial. We now describe the full enrollment of PIVOT and report the baseline characteristics of this study population.

METHODS

Design

PIVOT is a prospective, randomised, double-blind, placebo-controlled phase II clinical trial of hydroxyurea treatment for both children and adults with HbSC disease. The rationale and design of PIVOT have been published.[25]

Location

PIVOT is conducted in Accra, Ghana at Korle Bu Teaching Hospital (KBTH), the largest hospital in Ghana with over 2000 beds. KBTH is also a referral hospital for SCD and cares for a large group of affected children and adults. The paediatric SCD clinic cares for ~4000 patients up to 16 years of age, whilst the adolescent/adult clinic within the Ghana Institute of Clinical Genetics cares for ~10 000 patients.[26]

Population

Patients with HbSC disease followed at KBTH, age 5.00–49.99 years with steady-state laboratory values in the appropriate range, willingness to consent, and ability to comply with study procedures were eligible to enrol. Potential participants were temporarily excluded if they received a blood transfusion in the past 2 months, received hydroxyurea or other approved or investigational treatments for SCD in the past 6 months, received ≥6 blood transfusions in the past 12 months, or were hospitalised ≥10 times in the past 12 months. Patients who were pregnant, unable to tolerate hydroxyurea, or having underlying medical conditions that made study participation ill-advised were excluded.[25]

Intervention

After baseline studies were completed, participants were randomised to placebo or hydroxyurea as blinded study treatment at 20.0 ± 5.0 mg/kg/day. Randomisation was stratified by age (above and below age 18.0 years at consent) using a four-block design.

Study outcomes

The primary outcome is the cumulative incidence of haematological toxicities after 12 months of therapy, analysed by treatment assignment and age. Additional laboratory and clinical outcomes were collected at baseline to identify differences after 12 months of treatment that could be clinically meaningful and help determine the best end-points for a future phase III trial, including the following:

- Cumulative incidence of laboratory and clinical adverse events ≥grade 2 and serious adverse events (SAEs), graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, except for minor adjustments to laboratory grading due to the underlying nature of SCD as described in the previously published protocol.[25]
- Change from baseline in a variety of laboratory and clinical parameters
  - Cerebral Hb oxygen saturation
  - Three-dimensional splenic volume
  - Intracerebral arterial blood flow velocity
  - Grade of retinopathy
  - Whole blood viscosity
  - Erythrocyte deformability
  - Quality of life
  - Cumulative incidence of pain, acute chest syndrome, acute splenic sequestration, sepsis, malaria, stroke, and death
  - Cumulative incidence of blood transfusions and hospitalisations

Timeline

Participants were screened for 2 months before randomisation to hydroxyurea or placebo. Blinded study treatment is continued for 12 months, and then participants are invited to enrol in an open-label extension. The study is ongoing and will have a common termination date of 4 years from the time the first study participant initiated blinded treatment.

Sample size

PIVOT aimed to enrol 240 participants (~120 adults ≥18 years old and 120 children <18 years old) to allow for 10% screen failures and subsequent 8% dropout on treatment, yielding ~200 evaluable participants who complete 12 months of blinded study treatment. This number provides 80% power to detect a cumulative haematological toxicity rate of 20%, with a 15% margin for non-inferiority.

Data management

All study data during enrollment and screening were collected locally on paper case report forms and entered into REDCap Cloud, a secure, web-based, 21 CRF Part 11-compliant electronic data capture system. Baseline data included demographic characteristics, past medical history, physical examination, immunisation history, concomitant medications, and steady-state laboratory values. Medical history was self-reported by the participant and/or guardian.

Study measurements

Screening laboratory tests included a complete blood count and automated reticulocyte count (Mindray BC-6800, Shenzhen, China), serum chemistries (Mindray BS-430, Shenzhen, China), electrolytes (LMS-972, Shenzhen, China), urinalysis (URIT 10 V), and haemoglobin electrophoresis (SmartLife, PolyLC, Columbia, MD). Exploratory laboratory tests included ektacytometry for erythrocyte deformation and haemolysis (Lorrca, Mechatronics, Netherlands), OxygenScan to measure the point-of-sickling (Lorrca), and cone and plate viscometer to measure whole blood viscosity at 37C (DVNext, Brookfield/Ametek, Middleboro, MA). Screening tests to assess organ function included near-infrared spectroscopy cerebral oxygen saturation (Hemosphere Foresight, Edwards Lifesciences, LLC, Irvine, CA), transcranial Doppler ultrasonography for paediatric participants (SONARA/tek, Viasys Healthcare, Inc., Conshohocken, PA), retinal imaging (Optomed Aurora, Optomed Plc, Finland; Optos California, Optos Plc, UK; Optovue Ivue 80, Optovue Inc., USA), abdominal ultrasonography of the spleen and kidneys, and 6-minute walk test.[27] Quality of life was assessed using NIH-validated Patient-Reported Outcome Measurement Information

System (PROMIS) short forms for fatigue, pain, and pain interference.[28,29]

Genetic modifiers

Blood was preserved on a Flinders Technology Associates card and kept frozen at −80°C until transport to Cincinnati for DNA-based analysis. HbSC was confirmed genetically using TaqMan, whilst G6PD deficiency (A^- variant) and alpha thalassaemia trait (–3.7 kb deletion) were identified using PCR-based techniques.[30] Beta-globin haplotype was identified using a combination of TaqMan probes and restriction digestion patterns to identify the common haplotypes.[31]

Ethical considerations

Ethical approval was obtained from the KBTH-IRB (KBTH-IRB #0095/2021) and the Ghana FDA (FDA/HPT/SMC/CTD/CTA/22/0047). The study was also approved by the CCHMC IRB (2021–0520), but the KBTH board and Ghana FDA have primary oversight. Written informed consent was obtained from all patients age >17 years. For those ≤17 years, consent was obtained from a parent or guardian, and for those ages 10–17 years, assent was also obtained. Any child reaching 18 years of age whilst enrolled in the trial will be re-consented as an adult. PIVOT is registered with the Pan African Clinical Trials Registry (Trial ID PACTR202108893981080). An independent Data Safety Monitoring Board reviews the accumulating trial data twice annually.

RESULTS

Between April 2022 and June 2023, a total of 243 participants (123 paediatric <18 years old, 120 adult ≥18 years old) were enrolled. During screening 29 withdrew (Figure 1, CONSORT). Reasons for withdrawal included 19 not meeting eligibility criteria (17 HbSC not confirmed by HPLC, two with ineligible age), four withdrawn by the PI, three who withdrew consent, and three lost to follow-up. After the screening was completed, 214 participants were randomised (112 paediatric, 102 adult) and 56% were males. Two participants were withdrawn soon after randomisation when they were found to be ineligible (not HbSC).

Table 1 summarises baseline demographic, clinical, and laboratory characteristics. The full age range was captured in the cohort with the median age 21.6 years, range 5.0–49.1 years. At the time of enrollment, the vast majority of both children (76%) and adults (96%) reported previous vaso-occlusive painful events, and some reported acute chest syndrome (8% of children, 23% of adults). Prior malaria infection was common in both children (67%) and adults (95%). There was age-related accumulation of morbidity, with transfusions more common in adults (33%) than children (8%). Similarly, most children reported either no (13%) or ≤5 hospitalisations (83%), whereas 99% of adults reported at least one hospitalisation and 26% reported >20 lifetime hospitalisations. Baseline

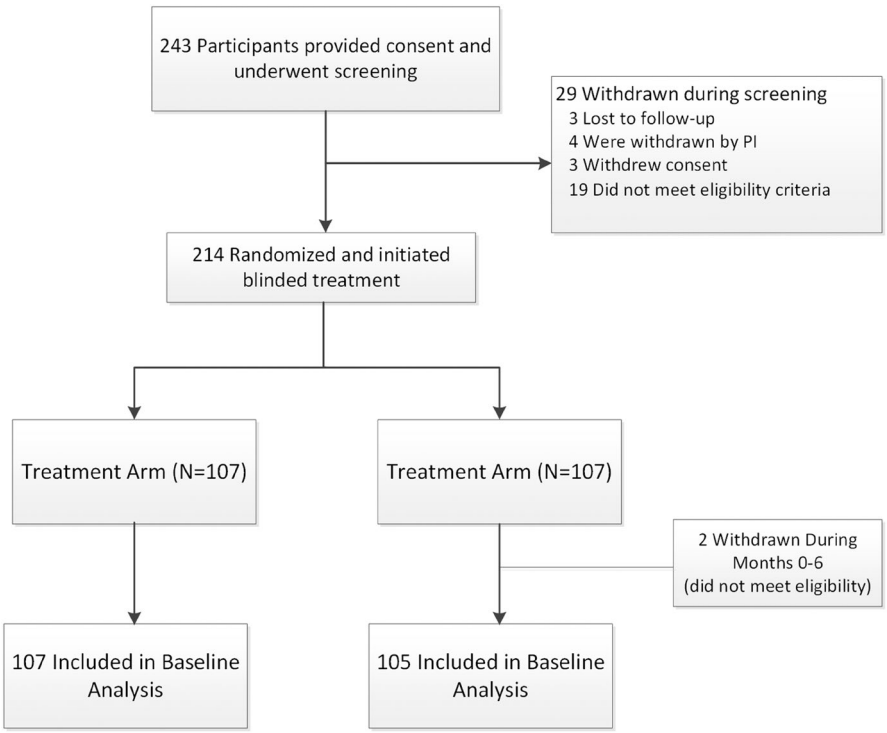

FIGURE 1 CONSORT diagram of participants enrolled in PIVOT.

TABLE 1 Baseline demographics, clinical, and laboratory characteristics of the randomised PIVOT participants.

	Children (<18 years)	Adults (≥18 years)	Total
Number of participants	112	100	212
Females (*N*, %)	40 (36)	53 (53)	93 (44)
Age at enrollment (years)	9.4 ± 3.0	35.0 ± 9.3	21.5 ± 14.5
Past medical history (*N*, %)			
Vaso-occlusive painful event	85 (76)	98 (96)	183 (86)
Dactylitis[a]	13 (12)	7 (10)	20 (11)
Malaria[b]	75 (67)	91 (95)	166 (80)
Acute chest syndrome[c]	9 (8)	20 (23)	29 (14)
Splenic sequestration[d]	1 (1)	1 (1)	2 (1)
Stroke	0 (0)	1 (1)	1 (0.5)
Previous hydroxyurea use[e]	1 (1)	1 (1)	2 (1)
Transfusion history (*N*, %)			
No previous transfusion	103 (92)	67 (67)	170 (80)
1–2 transfusions	9 (8)	25 (25)	34 (16)
3–5 transfusions	0 (0)	7 (7)	7 (3)
6–10 transfusions	0 (0)	1 (1)	1 (0.5)
Lifetime hospitalisations (*N*, %)			
No previous hospitalisation	14 (13)	1 (1)	15 (7)
≤5 hospitalisations	93 (83)	33 (33)	126 (59)
6–10 hospitalisations	4 (4)	21 (21)	25 (12)
10–20 hospitalisations	0 (0)	19 (19)	19 (9)
>20 hospitalisations	1 (1)	26 (26)	27 (13)
Physical exam			
Height (cm)	136 ± 17	166 ± 10	150 ± 21
Weight (kg)	30.7 ± 11.6	68.4 ± 13.3	48.5 ± 22.6
BMI (kg/m^2)	16.2 ± 2.9	25.1 ± 5.4	20.4 ± 6.2
Blood pressure—systolic (mm Hg)	103 ± 7	117 ± 12	109 ± 12
Blood pressure—diastolic (mm Hg)	65 ± 7	75 ± 9	70 ± 10
Oxygen saturation (%)	99 ± 1	98 ± 1	98 ± 1
Palpable spleen	3 (3)	0 (0)	3 (1)
Leg ulcers	0 (0)	0 (0)	0 (0)
Laboratory parameters			
Haemoglobin (g/dL)	10.6 ± 0.8	11.6 ± 1.4	11.0 ± 1.2
MCV (fL)	71 ± 6	77 ± 7	74 ± 7
MCHC (g/dL)	36.3 ± 0.7	36.1 ± 0.7	36.2 ± 0.7
Foetal haemoglobin (%)	2.5 ± 1.8	1.7 ± 1.4	2.1 ± 1.7
Absolute reticulocyte count (×10^9/L)	110 ± 129	104 ± 32	107 ± 96
White blood cells (×10^9/L)	8.2 ± 2.6	6.8 ± 2.8	7.5 ± 2.8
Absolute neutrophil count (×10^9/L)	3.8 ± 1.6	3.6 ± 2.0	3.7 ± 1.8
Platelets (×10^9/L)	287 ± 107	248 ± 120	269 ± 115
Creatinine (mg/dL)	0.6 ± 0.4	1.0 ± 0.5	0.8 ± 0.5
Alanine transferase (IU/L)	18 ± 11	21 ± 17	19 ± 14
Total bilirubin (mg/dL)	1.4 ± 0.7	1.6 ± 0.9	1.5 ± 0.8

Note: Values are provided as mean ± SD or frequency (proportion) unless otherwise noted.

Abbreviations: MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume.

[a]Out of 177 participants (108 children, 69 adults).

[b]Out of 208 participants (112 children, 96 adults).

[c]Out of 201 participants (112 children, 89 adults).

[d]Out of 199 participants (112 children, 87 adults).

[e]Out of 211 participants (112 children, 99 adults).

TABLE 2 Baseline assessment of organ function in the randomised PIVOT participants.

	Children (<18 years)		Adults (≥18 years)	Total
Number of participants	112		100	212
Transcranial Doppler[a]				
Time-averaged mean velocity	110 ± 19		-	-
Conditional	1 (1)		-	-
Abnormal	0 (0)		-	-
NIRS (%)[b]				
Left forehead	58 ± 9		49 ± 11	54 ± 11
Right forehead	58 ± 9		51 ± 13	55 ± 12
Non-proliferative retinopathy (*N*, %)				
Left eye, 1–3 abnormalities	12 (11)		13 (13)	25 (12)
Right eye, 1–3 abnormalities	15 (13)		13 (13)	28 (13)
Proliferative retinopathy (*N*, %)[c]				
Left eye, stage 1–2	32 (29)		41 (42)	73 (35)
Left eye, stage 3 or above	2 (2)		32 (33)	34 (16)
Right eye, stages 1–2	34 (30)		49 (51)	83 (40)
Right eye, stage 3 or above	3 (3)		24 (25)	27 (13)
6-minute walk				
Pretest oxygen saturation (%)	99 ± 1		97 ± 2	98 ± 2
Distance walked (metres)	524 ± 90		579 ± 116	550 ± 106
Post-test oxygen saturation (%)	97 ± 1		97 ± 2	97 ± 2
Splenic Ultrasonography[d]				
Spleen length (cm)	8.9 ± 1.7		11.2 ± 3.3	9.9 ± 2.7
Spleen volume (mL)	115.4 ± 71.3		220.1 ± 169.0	160.1 ± 133.1
Renal ultrasonography				
Left kidney length (cm)	9.0 ± 1.1		10.4 ± 0.8	9.6 ± 1.2
Right kidney length (cm)	8.5 ± 1.0		10.3 ± 0.8	9.4 ± 1.3
Urinalysis (*N*, %)				
Proteinuria present	1 (1)		0 (0)	1 (0.5)
Trace protein present	2 (2)		8 (8)	10 (5)
Quality of life				
Pain Intensity (*N*, %)	Child	Parent proxy	Adult	Total
No pain	20 (18)	18 (16)	62 (62)	80 (38)
1–2	83 (74)	86 (77)	18 (18)	104 (49)
3–10	6 (5)	8 (7)	19 (19)	27 (13)
No response	3 (3)	0 (0)	1 (1)	1 (0.5)
Pain interference, T-score (SE)[e]	39.3 (6.9)	42.7 (7.1)	46.5 (8.5)	44.5 (4.3)
Fatigue, T-score (SE)[f]	35.1 (7.6)	41.4 (8.6)	39.8 (9.7)	37.4 (4.3)

Note: Values are provided as mean ± SD (range) unless otherwise noted. Quality of life total values are an aggregate of parent proxy and adult values only.

Abbreviations: NIRS, near-infrared spectroscopy; SE, standard error.

[a]Measured on 111 children.

[b]Measured on 166 participants (90 children, 76 adults).

[c]Measured on 209 participants (112 children, 99 adults).

[d]Measured on 192 participants with observable spleens.

[e]Self-reported by 55 children, parent-reported for 111 children, and self-reported by 100 adults.

[f]Self-reported by 93 children, parent-reported for 71 children, and self-reported by 100 adults.

[Correction added on 29 October 2024, after first online publication: Data in the first two columns of "Pain interference, T-score (SE)[e]" and numbers of children in footnote "e" were corrected.]

haemoglobin concentration was slightly higher in adults (11.6 ± 1.4 g/dL) than in children (10.6 ± 0.8 g/dL), but HbF was low in both groups (2.5 ± 1.8 in children vs. 1.7 ± 1.4 in adults).

Table 2 summarises baseline organ function evaluations of the PIVOT cohort. TCD examinations in children were normal except for one conditional result. The mean mixed

TABLE 3 Baseline assessments of whole blood viscosity, erythrocyte ektacytometry, and point-of-sickling in the randomised PIVOT participants.

	Children (<18 years)	Adults (≥18 years)	Total
Number of participants	112	100	212
Whole blood viscosity (*N*)			
At shear rate of 75 s^{-1}	5.0 ± 0.7	5.9 ± 1.1	5.4 ± 1.0
At shear rate of 112.5 s^{-1}	4.8 ± 0.6	5.6 ± 0.9	5.2 ± 0.9
At shear rate of 185.7 s^{-1}	4.6 ± 0.5	5.3 ± 0.9	4.9 ± 0.8
At shear rate of 225 s^{-1}	4.6 ± 0.5	5.2 ± 0.9	4.8 ± 0.7
At shear rate of 300 s^{-1}	4.4 ± 0.4	4.9 ± 0.8	4.6 ± 0.7
Ektacytometry (*N*)[a]			
OsmoScan, O_{min}	97 ± 15	97 ± 16	97 ± 16
OsmoScan, O_{max}	196 ± 15	196 ± 16	196 ± 15
OsmoScan, O_{hyper}	332 ± 11	334 ± 12	333 ± 11
OxyScan, EI_{max}	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
OxyScan, Point-of-sickling (mm Hg)[b]	19.2 ± 7.4	19.5 ± 9.9	19.3 ± 8.6

Note: Values are provided as mean ± SD, (range) unless otherwise noted. Blood viscosity values are reported in centipoise (cP) at various shear rates (per second), whilst the Ektacytometry Elongation Index values are reported as the osmolality (mOsm/kg) at which each value is recorded. Point-of-sickling is reported as the partial pressure of oxygen (mm Hg) where the Elongation Index decreases to 95% of the EI_{max}.

[a]Analysed from 208 participants.

[b]Analysed from 207 participants.

cerebral oxygen saturation measured with NIRS was 58% in children and 51% in adults. Proliferative sickle retinopathy (PSR) was present at early Goldberg stages (stages 1–2) in 30% of children and 51% of adults, but more adults had ≥ stage 3 disease (33% adults, 3% children). Adults and children walked a similar distance during the 6-minute walk test with similar pre/post-oxygen saturation measurements. The spleen was detectable by ultrasonography in 98% of children and 82% of adults. Spleen length/volume and kidney length were greater in adults than in children. Trace proteinuria was detected in two children and eight adults. Quality of Life responses described slightly more pain in children than in adults; only 18% of children reported 'no pain' compared with 62% of adults. Pain interference and fatigue were slightly worse in adults (Table 2).

Exploratory laboratory end-points are summarised in Table 3. Whole blood viscosity at various shear stress values was slightly higher in adults than in children. Ektacytometry results were similar between adults and children, as were point-of-sickling values obtained during de-oxygenation. G6PD deficiency was identified in 20% of males and 2% of females. The heterozygous carrier state was identified in 31% of females. Alpha thalassaemia was also common, including 28% with a one-gene deletion and 2% with a two-gene deletion. The beta-globin haplotype was primarily the Benin and Central African Republic genotypes.

DISCUSSION

In this report, we document the breadth and severity of HbSC disease in a large group of children and adults in Ghana enrolled in the prospective PIVOT trial. Baseline assessments revealed substantial morbidity with numerous acute clinical complications across the age span, but especially amongst adults. Our evaluations support a recent retrospective chart review of adults living in Ghana with SCD, which reported that disease severity was common in those with HbSC, including recurrent pain, and that disease-modifying therapy would be recommended if these persons had HbSS disease.[19]

Previous cohort studies in the US and Jamaica have described the collective morbidity and mortality associated with HbSC,[10–12,14–16,32–37] but accurate descriptions of clinical complications, especially in adults, are limited. The CSSCD[32] reported acute pain episodes in HbSC requiring treatment at a medical facility, at an average rate of 0.4 episodes per patient-year but with great interpatient variability.[33] Amongst children with HbSC who enrolled in the CSSCD birth cohort, dactylitis, and acute pain episodes occurred occasionally before 1 year of age, and half experienced an acute pain episode requiring clinical evaluation and treatment by 7 years of age.[10] In PIVOT, prior painful vaso-occlusive events were reported in 76% of children with HbSC and almost all adults (96%). Because our medical history of pain was not restricted to previous episodes that required hospitalisation, the reported prevalence is similar to patient-reported pain described in daily diaries. Two large US-based studies conducted amongst children[38] and adults[39] asked patients to record any pain experienced in the past 24 h, regardless of the need for medication or health care utilisation. Half of the children with HbSC experienced pain in the first 4 years of life,[38] whilst adults with HbSC experienced pain equivalent to adults with HbSS regarding a day with a crisis or a day with health care utilisation.[39]

In our Ghanaian cohort, more children with HbSC reported pain than adults, which was unexpected and could reflect enrollment bias towards more affected children. Similarly, a history of acute chest syndrome was reported

in 8% of children and 23% of adults, roughly similar to a retrospective cross-sectional study at KBTH, in which 10% of adults 18–45 years old had a documented event in their medical record[19]; in the CSSCD, acute chest syndrome was reported in 40% of children with HbSC during the first decade of life, perhaps due to neonatal diagnosis and greater access to care.[10,34]

The overwhelming majority of participants (87% of children, 99% of adults) had been previously hospitalised before enrollment in PIVOT. Because hospitalisations were by patient report, we were unable to confirm the exact number and causes of these previous hospitalisations. This high cumulative incidence could reflect a recruitment bias towards sicker patients receiving care at a tertiary referral hospital, or perhaps patients who are well established with their current clinical team and find the hospital accessible, or possibly a higher overall disease burden for people living in Ghana where malaria and other diseases are common. In contrast to the high prevalence of hospitalisation, only 8% of children in our cohort had received a blood transfusion, which is lower than expected based on the CSSCD newborn cohort that reported 8% of children with HbSC had already received blood by age 5 years.[10] This could be due to differing transfusion practices in the US vs. Ghana, including acceptability and availability of safe and affordable transfusions.

Albuminuria is a recommended clinical trial end-point for organ dysfunction in SCD,[40] but evidence of sickle nephropathy with microalbuminuria was present in only a few children and adults enrolled in PIVOT. Our results are slightly lower than a previous cross-sectional study at KBTH in which 9% of children with HbSC had proteinuria.[41] Our methods were semi-quantitative and unable to determine a precise urine albumin/creatine ratio. The rate of macroalbuminuria detectable by urine dipstick is often lower in HbSC than in HbSS and increases with age.[42] In children with HbSC in high-income countries, macroalbuminuria occurred in only 1%–2%,[43,44] whilst macroalbuminuria was identified in 10%–20% of adults with HbSC.[45–47] Overt renal failure can occur in HbSC,[48] but the prevalence, cumulative incidence, and progression of albuminuria in HbSC is poorly defined. Even if hydroxyurea cannot reverse existing glomerular damage, early treatment might decrease sickling within the kidney and slow the development of proteinuria.[22]

PSR has consistently been identified with greater prevalence in HbSC than in HbSS,[18,49] and a previous study at KBTH documented substantial eye disease in HbSC disease.[50] Age-related accumulation of proliferative eye disease was initially described in the Jamaican cohort amongst subjects 5–26 years old,[17] and subsequent clinical trials for the treatment of PSR documented visual loss in 10% of untreated eyes.[51] In PIVOT, we detected a large burden of peripheral retinal disease especially in adults, with almost half having PSR and 33% with ≥ stage 3 disease, and we will investigate the onset of PSR and differences in progression between treatment arms in this large cohort of adults and children.

Baseline laboratory results were consistent with cross-sectional descriptions from the CSSCD cohort.[8] Our additional measurements of whole blood viscosity, red cell deformability in an osmolar gradient, and oxygen gradient ektacytometry provide much more data than previously reported in HbSC[52–57] and will explore the effects of hydroxyurea treatment. Blood viscosity in HbSC disease is higher than in both HbSS disease and normal controls with HbAA.[54,55] This is partly due to the higher haemoglobin concentration in HbSC disease, but also due to an RBC population that is more denser and less deformable. Our results confirm an elevated whole blood viscosity in a large group of participants with HbSC disease prior to randomisation. Hydroxyurea could increase the haemoglobin concentration and increase blood viscosity, with a predicted higher risk of clinical complications. However, due to reduction in leucocyte and platelet counts, hydroxyurea may actually lower the whole blood viscosity.[57]

The rationale for hydroxyurea treatment in HbSC disease is based on similarities in pathophysiology to HbSS, recognising there are also important differences. Erythrocytes containing HbS and HbC are prone to intracellular sickling in deoxygenating conditions but additionally tend towards intracellular crystal formation and cellular dehydration. Loss of water within the erythrocytes leads to hyperdense cells (higher MCHC) that are prone to HbS polymerisation and increased blood viscosity.[58,59] In contrast to HbSS; however, the role of HbF as a protective anti-sickling haemoglobin in HbSC is unclear.

HbSC is often said to be milder than HbSS, and with this moniker is sometimes misunderstood to be a 'mild' disease with infrequent complications. Our PIVOT baseline results document clearly that this is untrue, especially in sub-Saharan Africa; HbSC disease incurs greater morbidity and mortality than many other non-communicable diseases and deserves a robust, organised, and collective effort to identify treatments that decrease suffering and prolong healthy life. Hydroxyurea is an obvious choice because of its availability, cost, and likely benefit. Now fully enrolled, the PIVOT cohort has already contributed information on a large group of people living with HbSC disease. The future results will help identify an appropriate end-point for a future phase III trial.

AUTHOR CONTRIBUTIONS

REW conceptualised the trial. REW, SES, YDA, CIS, LRS, KDT, TSL, and KNAA contributed to the design. REW and SES wrote the protocol. REW secured the funding. CIS, YDA, LRS, and REW supervised the trial. REW, TSL, ACL, and LRS analysed the data. CIS, LRS, and REW drafted the first version of the manuscript. CIS, LRS, SES, KNAA, KDT, PE, EM, ACL, WG, LGT, AO, EA, TSL, YADA, and REW conducted the trial, critically reviewed and edited the manuscript, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

REW is a board member for the Foundation of Women and Girls with Blood Disorders (unpaid); receives hydroxyurea donated for two research studies from Theravia; serves on a Medical Advisory Board for Merck Pharmaceuticals and Theravia; and participates on Data and Safety Monitoring Boards for Novartis and Vaxart, Inc. The study treatments were provided by Theravia, but the clinical trial and manuscript preparation were conducted without the influence of any sponsors. All other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

De-identified individual participant data that underlie the reported results will be made available 3 months after publication for a period of 36 months after the publication date. Requests for de-identified participant data may be directed to the russell.ware@cchmc.org and must include an IRB-approved proposal. De-identified data will be made available following approval by an internal review committee and the execution of a data-sharing agreement between all parties.

ETHICAL APPROVAL

Ethical approval was obtained from the KBTH-IRB (KBTH-IRB #0095/2021) and the Ghana FDA (FDA/HPT/SMC/CTD/CTA/22/0047). The study was also approved by the CCHMC IRB (2021–0520), but the KBTH board and Ghana FDA have primary oversight.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all patients aged >17 years. For those ≤17 years, consent was obtained from a parent or guardian, and for those ages 10–17 years, assent was also obtained. Any child reaching 18 years of age whilst enrolled in the trial will be re-consented as an adult.

CLINICAL TRIAL REGISTRATION

PIVOT is registered with the Pan African Clinical Trials Registry (Trial ID PACTR202108893981080).

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REFERENCES

1. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390(10091):311–23.
2. GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the global burden of disease study 2021. Lancet Haematol. 2023;10(8):e585–e599.
3. Nagel RL, Fabry ME, Steinberg MH. The paradox of hemoglobin SC disease. Blood Rev. 2003;17(3):167–78.
4. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38(4 Suppl):S512–S521.
5. Therrell BL Jr, Lloyd-Puryear MA, Eckman JR, Mann MY. Newborn screening for sickle cell diseases in the United States: a review of data spanning 2 decades. Semin Perinatol. 2015;39(3):238–51.
6. Dufrenot MM, Legait JP, Traore A. Contribution a l'etude de la Reparition des Genes S et C Hemoglobiniques en Haute-Volta, au Mali et au Niger. Bull Soc Pathol Exot Filiales. 1970;63(5):606–14.
7. Segbefia CI, Goka B, Welbeck J, Amegan-Aho K, Dwuma-Badu D, Rao S, et al. Implementing newborn screening for sickle cell disease in Korle Bu teaching hospital, accra: results and lessons learned. Pediatr Blood Cancer. 2021;68(7):e29068.
8. West MS, Wethers D, Smith J, Steinberg M. Laboratory profile of sickle cell disease: a cross-sectional analysis. The cooperative study of sickle cell disease. J Clin Epidemiol. 1992;45(8):893–909.
9. Brown AK, Sleeper LA, Miller ST, Pegelow CH, Gill FM, Waclawiw MA. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Cooperative study of sickle cell disease. Arch Pediatr Adolesc Med. 1994;148(8):796–804.
10. Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative study of sickle cell disease. Blood. 1995;86(2):776–83.
11. Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative study of sickle cell disease. Pediatrics. 1989;84(3):500–8.
12. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–44.
13. Stevens MC, Maude GH, Beckford M, Grandison Y, Mason K, Serjeant BE, et al. Haematological change in sickle cell-haemoglobin C disease and in sickle cell-beta thalassaemia: a cohort study from birth. Br J Haematol. 1985;60(2):279–92.
14. Rogers DW, Clarke JM, Cupidore L, Ramlal AM, Sparke BR, Serjeant GR. Early deaths in Jamaican children with sickle cell disease. Br Med J. 1978;1(6126):1515–6.
15. Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle-cell disease in Jamaica. Br Med J (Clin Res Ed). 1982;285(6342):633–5.
16. Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH, et al. Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med. 1991;325(21):1476–81.
17. Downes SM, Hambleton IR, Chuang EL, Lois N, Serjeant GR, Bird AC. Incidence and natural history of proliferative sickle cell retinopathy: observations from a cohort study. Ophthalmology. 2005;112(11):1869–75.

18. Nelson M, Noisette L, Pugh N, Gordeuk V, Hsu LL, Wun T, et al. The clinical spectrum of HbSC sickle cell disease-not a benign condition. Br J Haematol. 2024;205(2):653–63.
19. Ghunney WK, Asare EV, Ayete-Nyampong JB, Oppong SA, Rodeghier M, DeBaun MR, et al. Most adults with severe HbSC disease are not treated with hydroxyurea. Blood Adv. 2023;7(13):3312–9.
20. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033–48.
21. Savage WJ, Buchanan GR, Yawn BP, Afenyi-Annan AN, Ballas SK, Goldsmith JC, et al. Evidence gaps in the management of sickle cell disease: a summary of needed research. Am J Hematol. 2015;90(4):273–5.
22. Iyer R, Baliga R, Nagel RL, Brugnara C, Kirchner K, Hogan S, et al. Maximum urine concentrating ability in children with Hb SC disease: effects of hydroxyurea. Am J Hematol. 2000;64(1):47–52.
23. Miller MK, Zimmerman SA, Schultz WH, Ware RE. Hydroxyurea therapy for pediatric patients with hemoglobin SC disease. J Pediatr Hematol Oncol. 2001;23(5):306–8.
24. Luchtman-Jones L, Pressel S, Hilliard L, Brown RC, Smith MG, Thompson AA, et al. Effects of hydroxyurea treatment for patients with hemoglobin SC disease. Am J Hematol. 2016;91(2):238–42.
25. Smart LR, Segbefia CI, Latham TS, Stuber SE, Amissah-Arthur KN, Dzefi-Tettey K, et al. Prospective identification of variables as outcomes for treatment (PIVOT): study protocol for a randomised, placebo-controlled trial of hydroxyurea for Ghanaian children and adults with haemoglobin SC disease. Trials. 2023;24(1):603.
26. Asare EV, Wilson I, Benneh-Akwasi Kuma AA, Dei-Adomakoh Y, Sey F, Olayemi E. Burden of sickle cell disease in Ghana: the Korle-Bu experience. Adv Hematol. 2018;2018:6161270.
27. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428–46.
28. Dampier C, Barry V, Gross HE, Lui Y, Thornburg CD, DeWalt DA, et al. Initial evaluation of the pediatric PROMIS® health domains in children and adolescents with sickle cell disease. Pediatr Blood Cancer. 2016;63(6):1031–7.
29. Curtis S, Brandow AM. Responsiveness of patient-reported outcome measurement information system (PROMIS) pain domains and disease-specific patient-reported outcome measures in children and adults with sickle cell disease. Hematology Am Soc Hematol Educ Program. 2017;2017(1):542–5.
30. Smart LR, Ambrose EE, Balyorugulu G, Songoro P, Shabani I, Komba P, et al. Stroke prevention with hydroxyurea enabled through research and education: a phase 2 primary stroke prevention trial in sub-Saharan Africa. Acta Haematol. 2023;146(2):95–105.
31. McGann PT, Williams TN, Olupot-Olupot P, Tomlinson GA, Lane A, Luís Reis da Fonseca J, et al. Realizing effectiveness across continents with hydroxyurea: enrollment and baseline characteristics of the multicenter REACH study in sub-Saharan Africa. Am J Hematol. 2018;93(4):537–45.
32. Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. Am J Pediatr Hematol Oncol. 1982;4(2):197–201.
33. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, et al. Pain in sickle cell disease. Rates and risk factors. N Engl J Med. 1991;3 25(1):11–6.
34. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The cooperative study of sickle cell disease. Blood. 1994;84(2):643–9.
35. Rezende PV, Santos MV, Campos GF, Vieira LLM, Souza MB, Belisário AR, et al. Clinical and hematological profile in a newborn cohort with hemoglobin SC. J Pediatr. 2018;94(6):666–72.
36. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010;115(17):3447–52.
37. Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica. 2007;92(7):905–12.
38. Dampier C, Ely B, Brodecki D, Coleman C, Aertker L, Sendecki JA, et al. Pain characteristics and age-related pain trajectories in infants and young children with sickle cell disease. Pediatr Blood Cancer. 2014;61(2):291–6.
39. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148(2):94–101.
40. Farrell AT, Panepinto J, Desai AA, Kassim AA, Lebensburger J, Walters MC, et al. End points for sickle cell disease clinical trials: renal and cardiopulmonary, cure, and low-resource settings. Blood Adv. 2019;3(23):4002–20.
41. Osei-Yeboah CT, Rodrigues O. Renal status of children with sickle cell disease in Accra, Ghana. Ghana Med J. 2011;45(4):155–60.
42. Ataga KI, Derebail VK, Archer DR. The glomerulopathy of sickle cell disease. Am J Hematol. 2014;89(9):907–14.
43. Wigfall DR, Ware RE, Burchinal MR, Kinney TR, Foreman JW. Prevalence and clinical correlates of glomerulopathy in children with sickle cell disease. J Pediatr. 2000;136(6):749–53.
44. Lionnet F, Hammoudi N, Stojanovic KS, Avellino V, Grateau G, Girot R, et al. Hemoglobin sickle cell disease complications: a clinical study of 179 cases. Haematologica. 2012;97(8):1136–41.
45. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006;17(8):2228–35.
46. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. N Engl J Med. 1992;326(14):910–5.
47. Drawz P, Ayyappan S, Nouraie M, Saraf S, Gordeuk V, Hostetter T, et al. Kidney disease among patients with sickle cell disease, hemoglobin SS and SC. Clin J Am Soc Nephrol. 2016;11(2):207–15.
48. Powars DR, Hiti A, Ramicone E, Johnson C, Chan L. Outcome in hemoglobin SC disease: a four-decade observational study of clinical, hematologic, and genetic factors. Am J Hematol. 2002;70(3):206–15.
49. Amissah-Arthur KN, Mensah E. The past, present and future management of sickle cell retinopathy within an African context. Eye (Lond). 2018;32(8):1304–14.
50. Osafo-Kwaako A, Kimani K, Ilako D, Akafo S, Ekem I, Rodrigues O, et al. Ocular manifestations of sickle cell disease at the Korle-bu hospital, Accra, Ghana. Eur J Ophthalmol. 2011;21(4):484–9.
51. Moriarty BJ, Acheson RW, Condon PI, Serjeant GR. Patterns of visual loss in untreated sickle cell retinopathy. Eye (Lond). 1988;2(Pt 3):330–5.
52. Boisson C, Rab MAE, Nader E, Renoux C, Kanne C, Bos J, et al. Effects of genotypes and treatment on Oxygenscan parameters in sickle cell disease. Cells. 2021;10(4):811.
53. Boisson C, Rab MAE, Nader E, Renoux C, van Oirschot BA, Joly P, et al. Methodological aspects of oxygen gradient ektacytometry in sickle cell disease: effects of sample storage on outcome parameters in distinct patient subgroups. Clin Hemorheol Microcirc. 2021;77(4):391–4.
54. Renoux C, Romana M, Joly P, Ferdinand S, Faes C, Lemonne N, et al. Effect of age on blood rheology in sickle cell anaemia and sickle cell haemoglobin C disease: a cross-sectional study. PLoS One. 2016;11(6):e0158182.
55. Tripette J, Alexy T, Hardy-Dessources MD, Mougenel D, Beltan E, Chalabi T, et al. Red blood cell aggregation, aggregate strength and oxygen transport potential of blood are abnormal in both homozygous sickle cell anemia and sickle-hemoglobin C disease. Haematologica. 2009;94(8):1060–5.
56. Boisson C, Nader E, Renoux C, Gauthier A, Poutrel S, Bertrand Y, et al. Shear-stress-gradient and oxygen-gradient ektacytometry in

sickle cell patients at steady state and during vaso-occlusive crises. Cells. 2022;11(3):585.
57. Lemonne N, Charlot K, Waltz X, Ballas SK, Lamarre Y, Lee K, et al. Hydroxyurea treatment does not increase blood viscosity and improves red blood cell rheology in sickle cell anemia. Haematologica. 2015;100(10):e383–e386.
58. Fabry ME, Kaul DK, Raventos-Suarez C, Chang H, Nagel RL. SC erythrocytes have an abnormally high intracellular hemoglobin concentration. Pathophysiological consequences. J Clin Invest. 1982;70(6):1315–9.
59. Bunn HF, Noguchi CT, Hofrichter J, Schechter GP, Schechter AN, Eaton WA. Molecular and cellular pathogenesis of hemoglobin SC disease. Proc Natl Acad Sci USA. 1982;79(23):7527–31.

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