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Pain and Other Non-Neurological Adverse Events in Children with Sickle Cell Anemia and Previous Stroke who Received Hydroxyurea and Phlebotomy or Chronic Transfusions and Chelation: Results from the SWITCH Clinical Trial

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Abstract

Purpose—To compare the non-neurological events in children with sickle cell anemia (SCA) and previous stroke enrolled in SWITCH.

Methods—The NHLBI-sponsored Phase III multicenter randomized clinical trial *Stroke With Transfusions Changing to Hydroxyurea* (SWITCH) (ClinicalTrials.gov NCT00122980) compared continuation of chronic blood transfusion/iron chelation to switching to hydroxyurea/phlebotomy for secondary stroke prevention and management of iron overload. All randomized children were included in the analysis (intention to treat). The Fisher's Exact test was used to compare the frequency of subjects who experienced at least one SCA-related adverse event (AE) or serious adverse event (SAE) in each arm and to compare event rates.

Results—133 subjects, mean age 13 ±3.9 years (range 5.2–19.0 years) and mean time of 7 years on chronic transfusion at study entry, were randomized and treated. Numbers of subjects

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experiencing non-neurological AEs were similar in the two treatment arms, including SCA-related events, SCA pain events, and low rates of acute chest syndrome and infection. However, fewer children continuing transfusion/chelation experienced SAEs ($p=0.012$), SCA-related SAEs ($p=0.003$), and SCA pain SAEs ($p=0.016$) as compared to children on the hydroxyurea/phlebotomy arm. The timing of phlebotomy did not influence SAEs. Older age at baseline predicted having at least 1 SCA pain event. Patients with recurrent neurological events during SWiTCH were not more likely to experience pain.

Conclusions—In children with SCA and prior stroke, monthly transfusions and daily iron chelation provided superior protection against acute vaso-occlusive pain SAEs when compared to hydroxyurea and monthly phlebotomy.

Keywords

sickle cell anemia; hydroxyurea; transfusion; pain; acute chest syndrome

INTRODUCTION

Chronic transfusions and hydroxyurea are commonly used preventive treatments for sickle cell anemia (SCA). Chronic transfusion therapy is the standard of care to prevent a first stroke once an increased risk is detected by an abnormal transcranial Doppler ultrasound [1, 2], or to prevent recurrent stroke [3]; chronic transfusion therapy is also effective in reducing the frequency of pain and acute chest syndrome (ACS) [4, 5]. Because of risks associated with blood transfusions, such as iron overload, alloimmunization, and transfusion reactions [6], other therapeutic options for the prevention of stroke are desirable and require exploration.

Hydroxyurea, a drug that increases fetal hemoglobin level and decreases red cell adhesion to the endothelium [7] among other physiologic effects, is an attractive alternative to transfusion for clinical complications including stroke prevention. Hydroxyurea reduces pain, ACS, hospitalizations, and transfusion requirements, and increases survival rates in adults with SCA; it is FDA approved for use in adults with SCA. [8-11]. Similar efficacy and a favorable safety profile have recently been documented in infants and young children [12]. Furthermore, single institution pilot data suggested that hydroxyurea may reduce stroke recurrence in children [13].

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH), a prospective Phase III multi-center NHLBI-sponsored study (NCT00122980), compared hydroxyurea with phlebotomy and chronic transfusions with iron chelation for prevention of secondary stroke and management of iron overload. The trial was ended early when an interim analysis documented no difference in the liver iron concentration (LIC) between the 2 treatment arms and strokes in the hydroxyurea with phlebotomy arm whereas there were no strokes on the transfusion with chelation arm [14]; thus, transfusion with iron chelation remain the best way to manage children with SCA, stroke, and iron overload. We have analyzed SWiTCH data to determine whether there were differences in the frequency of non-neurological events between the two treatment arms. To date, there have been no prospective studies comparing blood transfusions to hydroxyurea for the prevention of such complications.

METHODS

Subjects and Study Treatments

The study was approved by the local Institutional Review Board at each of the 25 clinical sites, and informed consent and assent (children ages 7-17) were obtained prior to participation. The design of the study has been previously described [15]. Subjects 5.0-18.9 years of age with a diagnosis of hemoglobin SS, hemoglobin S- β^0 thalassemia, or hemoglobin S-O_{Arab} and prior documented stroke were eligible for participation and randomization in a 1:1 fashion to either treatment arm if they had received at least 18 months of chronic transfusions after the index stroke and had documented iron overload, defined by LIC > 5 mg/g dry weight liver on baseline liver biopsy. The details of the study procedures have been previously described [14]; a brief description of the treatment arms is presented below.

The Standard Transfusion/Chelation treatment arm—Those randomized to the standard treatment arm continued erythrocyte transfusions each month (every 4 weeks $\pm$ 1 week) by simple transfusion, a partial exchange technique, or automated erythrocytapheresis, according to the local investigator's discretion. The target for pre-transfusion hemoglobin (Hb) S was below 30%. Oral deferasirox was the primary iron chelator used in the management of transfusional iron overload, and was given at a dose of 20-40 mg/kg administered as dispersible tablets once a day. Three subjects received subcutaneous deferoxamine during the study instead of deferasirox.

The Alternative Hydroxyurea/Phlebotomy treatment arm—Hydroxyurea was the therapy used to prevent secondary stroke in this arm. Hydroxyurea was administered under an Investigational New Drug Application (IND) in this study, as it is not FDA approved for use in children with SCA. For subjects randomized to hydroxyurea, therapy was begun at a dose of 20 mg/kg/day and escalated at two-month intervals to achieve an increase in hemoglobin F, erythrocyte macrocytosis and a reduction in leukocyte counts. The target absolute neutrophil count (ANC) was $2.0-4.0 \times 10^9/L$. The maximum hydroxyurea dose allowed was 35 mg/kg/day or 2 grams daily. During the hydroxyurea dose escalation to maximum tolerated dose (MTD), transfusions were continued per protocol to reduce the risk of secondary stroke (overlap period). However, the transfusion target hemoglobin concentration was progressively lowered to allow endogenous erythropoiesis to continue under the influence of the hydroxyurea therapy. Once the hydroxyurea MTD was reached, transfusions were discontinued. After this point, children underwent monthly therapeutic phlebotomy to manage iron overload; iron chelation was not prescribed. A total of 5-10 mL/kg of blood (maximum 500 mL) was removed every 4 weeks ($\pm$ 1 week) as tolerated, with immediate volume replacement with normal saline.

Study Endpoints

The primary composite endpoint of the Phase III randomized SWiTCH trial was to compare 30 months of alternative therapy (hydroxyurea and phlebotomy) with standard therapy (transfusions and chelation) for the prevention of secondary stroke and the reduction of transfusional iron overload in pediatric subjects with SCA and previous stroke. In order for

the alternative treatment regimen to be non-inferior to the standard treatment regimen, the hydroxyurea-treated group needed to have both a recurrent stroke rate similar to that of the transfusion-treated group and a greater reduction in liver iron stores. The results of these analyses are summarized elsewhere [14].

One of the secondary endpoints, and the focus of this paper, was to compare rates of non-neurological SCA-related events (e.g., vaso-occlusive pain, ACS, splenic sequestration, priapism) and non-SCA-related adverse events in each treatment arm.

Definition of Adverse Events and Serious Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a study subject that did not necessarily have a causal relationship with treatment administered in the study. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study. AEs are the superordinate category including non-serious and serious adverse events (SAE). AEs were also classified as SCA-related or not SCA-related according to the investigator's opinion. SCA-related AEs included, but were not limited to, pain associated with vaso-occlusion and ACS. Sickle cell pain was an expected adverse event. Pain attributed to SCA was reported even if the event was not evaluated at a medical facility. ACS required at least 3 of the following symptoms: chest pain, fever over 38.5°C, tachypnea, wheezing, or cough. A new pulmonary infiltrate must have been present on chest X-ray involving at least 1 complete lung segment, suggestive of alveolar consolidation and not atelectasis.

An SAE was defined in SWiTCH as an AE that: (1) Resulted in death; (2) Was life-threatening; (3) Required inpatient hospitalization of > 4 days or prolongation of existing hospitalization; (4) Resulted in persistent or significant disability/incapacity; or anomaly/birth defect; or (5) Was an important medical event in the opinion of the clinical investigator. The SWiTCH Medical Monitor reviewed all SAEs.

Adverse events were coded using the Medical Dictionary of Regulatory Affairs (MedDRA), version 9.1. Events are summarized/analyzed using the categories of System Organ Class and Preferred Term. For this analysis, stroke and other neurological AEs were excluded.

Statistical Analysis

All randomized SWiTCH subjects were included in the data analysis (intention to treat, ITT). Numbers of subjects experiencing at least one event in a specified adverse event category were compared between treatment groups using a Fisher's Exact test.

Sickle cell-related clinical events recorded were body pain (subsequently referred to as SCA pain), ACS, cholelithiasis, infections, priapism, among others. For subjects randomized to hydroxyurea, all events occurring from randomization through completion/discontinuation of the treatment period of the study were tabulated, including those occurring during the hydroxyurea/transition overlap period for subjects randomized to the Alternative Treatment Arm.

For event rates (events per person year) of AEs, SAEs, SCA-related AEs and SAEs, SCA pain AEs and SAEs, we computed mean and median event rates, confidence intervals, and risk ratios. In addition to the overall computation of these statistics by treatment group, these statistics were computed for two additional time frames in the Hydroxyurea/Phlebotomy group: the initial transfusion overlap period and the post-transfusion period when subjects were solely on Hydroxyurea/Phlebotomy. The overlap period was defined as that period of time in the alternative arm when the subjects were receiving blood transfusions and hydroxyurea until the first phlebotomy procedure (usually 1 month after last transfusion) was performed.

Logistic regression using repeated measures was employed to evaluate the effects of various laboratory parameters (i.e., ALT, AST, total bilirubin, serum creatinine, LIC, serum ferritin, hemoglobin, hematocrit, Hb A, Hb F, Hb S, MCV, white cell count, and LDH) on the likelihood of experiencing an SCA pain event. Specifically, we compared (via a computer algorithm) various laboratory values assessed 1-5 days *before* an SCA event to the remaining laboratory values that were not chronologically associated with an SCA pain event. The predictive ability of each laboratory parameter was evaluated with a separate model that also included treatment group and age at consent as factors. Logistic regression, controlling for treatment group and age at consent (when not otherwise included in the model), was also used to analyze the ability of continuous clinical parameters (i.e., age at consent, treatment compliance with hydroxyurea, treatment compliance with chelation, and prior erythrocyte antibodies) to predict whether or not a subject would have an SCA pain event at any time while on treatment. The effects of gender, alpha thalassemia deletion (yes or no), and CAR haplotype (yes or no) on likelihood of a pain event were evaluated via individual chi-square test, controlling for treatment group.

Once predictors of SCA pain events were individually identified, they were added together into a logistical regression model to determine which parameters uniquely contributed to predicting an SCA pain event.

P-values were not adjusted for multiplicity.

RESULTS

There were 134 randomized subjects in SWITCH; 67 in each arm. One subject randomized to blood transfusion exited the study before treatment intervention for a total of 66 subjects in the standard arm; the ITT population therefore includes 133 subjects. Overall mean age was 13 ± 3.8 (range 5.2-19.0 years) at enrollment; 54% were males. Subjects had on average 7 years of chronic transfusions for secondary stroke prevention prior to study entry.

Table I presents basic demographics and mean hemoglobin values by treatment group for the ITT population at study entry and exit. Those on hydroxyurea achieved a significant rise in fetal hemoglobin. All differences in hemoglobin S, A, and F at study exit were expected and were related to study treatment. A total of 60 of 67 subjects on the alternative arm reached hydroxyurea MTD, had transfusions discontinued and moved to the phlebotomy phase. Six hydroxyurea subjects discontinued participation prior to the transition (1 due to

an adjudicated stroke, 3 for non-adherence, 1 because study terminated prior to transition, 1 subject requested to withdraw). One completed the study without ever making the transition due to poor treatment adherence. Because the study was terminated early, only 50 subjects completed the planned 30 months; however, the average number of months on protocol-directed treatment was 23.4 ± 7.4 (range 5.12-31.9) for both arms, which allows meaningful conclusions regarding differences between both treatment arms.

Adverse Events

There were 1253 AEs post-randomization, excluding nervous system events; (4.8 events per person-year of exposure), and these events occurred in 128 (96.2%) subjects. Table II lists the number of subjects experiencing non-neurological AEs by treatment arm, along with the count of events. There was no difference between treatment groups in the number of subjects experiencing an AE, SCA-related AE, SCA pain AE (which were coded and summarized separately as “sickle cell anemia with crisis”), or in the individual musculoskeletal complaints: arthralgia, pain in extremity, back pain, muscular weakness or pain, musculoskeletal chest pain, and evidence of osteonecrosis. More subjects on standard treatment (n=8) had AEs related to the immune system (5 with hypersensitivity, 1 allergy to arthropod, 1 anaphylactic reaction, and 1 drug hypersensitivity) as compared to 1 subject with hypersensitivity reaction in the alternative arm; $p=0.017$.

Regarding laboratory AEs, more subjects on chronic transfusions experienced hyperbilirubinemia (beyond the expected levels for this subject population defined in the study as a total bilirubin >5 mg/dL (grade 2)) and SCA-related hyperbilirubinemia (as explicitly characterized by the investigator), suggesting more hemolysis or cholestasis. Liver function AEs (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) were not different between the treatment groups. More subjects in the Hydroxyurea/Phlebotomy arm experienced treatment-related cytopenias with median highest severity grade 2: reticulocytopenia ($p=0.001$), neutropenia ($p=0.009$), and anemia ($p=0.001$). Non-statistically significant differences were seen for thrombocytopenia. These are expected hematologic effects of hydroxyurea and were predominantly “moderate” in severity. None of the hematological AE was serious. No subjects experienced fever and neutropenia or bacteremia related to neutropenia.

Serious Adverse Events

Table III details the count of subjects experiencing various non-neurological SAEs per treatment arm, along with the annualized rate of events. Thirty-eight subjects had a total of 81 SAEs, with significantly more subjects in the alternative treatment arm (n=26; 38.8%) than subjects on the standard arm (n=12; 18.2%; $p=0.012$) experiencing an SAE. Two SAEs resulted in death: 1 in each treatment arm. The causes of death were pulmonary embolism in the subject who continued on Transfusion/Chelation and intracranial bleeding in the subject who switched to Hydroxyurea/Phlebotomy. Although one of those two deaths was neurological, it has been included in this paragraph for completeness.

There were a total of 61 non-neurological, SCA-related SAEs during the study treatment period, experienced by 3-times as many subjects in the alternative arm (n=22; 32.8%) as

compared to the standard arm ($n=7$; 10.6%; $p=0.003$). Most of the SAEs in both treatment groups were SAEs due to prolonged hospitalization (>4 days) for sickle-related pain (76 events). Six of the events were also considered by the site investigator to be life-threatening: SCA pain crisis, status asthmaticus (both occurred concurrently in the same subject), septic shock, and a complex of 3 events in the same subject: Klebsiella sepsis, urosepsis, and systemic inflammatory response.

Although there was no significant difference in the length of hospitalization between both treatment arms (4.3 ± 3.3 days vs. 3.8 ± 2.4 days for the standard and alternative arms, respectively), there was a significant treatment group difference in the number of subjects experiencing a serious SCA pain event (i.e., requiring more than 4 days of hospitalization). More children in the Hydroxyurea/Phlebotomy arm ($n=16$; 23.9%) experienced a pain SAE than did children in the Transfusion/Chelation arm ($n=5$; 7.6%; $p=0.016$). In the Hydroxyurea/Phlebotomy arm, there were twice as many pain events after transfusions were ended, as compared to during the overlap period. There was no temporal relationship between the pain events and blood transfusions, regardless of treatment group, or between pain events and phlebotomy procedures.

ACS events were few, and there were no treatment group differences in ACS AEs or SAEs (subset of events requiring >4 days of hospitalization; see Tables II and III). None of the ACS episodes required ventilator assistance.

The number of subjects with infection SAEs was not significantly different between the treatment arms ($p=0.165$). Only 1 infection was associated with a central line. There were seven episodes of SAE infection in the alternative arm: 2 cases of pyelonephritis (one of which also included *Escherichia coli* bacteremia) and 1 episode each of cytomegalovirus infection, infusion site infection, Mycoplasma infection, pneumonia, septic shock, and Staphylococcal infection. There were 2 infections SAEs in the standard arm: 1 gastroenteritis and 1 Klebsiella sepsis with urosepsis.

Annualized Rates of AEs and SAEs

Table IV provides a summary and analysis of annualized rates of non-neurological AEs and SAEs. The events that occurred to subjects participating in the Alternative Treatment Arm were analyzed for the overall treatment period and also divided into overall, overlap, and post-overlap observation. For all categories, annualized rates of events were significantly higher in the Hydroxyurea/Phlebotomy group whether or not the overlap period was included in the analysis.

Predictors of SCA Pain

Analysis of clinical predictors of whether or not a subject would experience an SCA pain event at any time during the study, revealed a significant effect for age at consent ($p=0.004$), with older subjects more likely to experience at least 1 SCA pain event during the study. The mean age at consent for those children who experienced a pain SAE was 14.6 ± 3.5 years and the mean age of children who did not was 12.9 ± 3.9 years. Adherence to treatment evidenced by pill counts (hydroxyurea, deferasirox), gender, duration of prior transfusion at baseline, alpha thalassemia deletion, CAR haplotype, baseline liver iron concentration, and prior red-

cell antibody status did not predict an on-study pain event, when controlling for age at consent.

Subjects who had transient ischemic attacks (N=17) or recurrent stroke on-study (N=7) were not more likely to experience on-study pain events ($p=0.356$, $p=0.981$, respectively). There were a number of laboratory parameters that were individually evaluated and found to be predictive or to have a temporal relationship with SCA pain (including both non-serious and serious events). Lower hemoglobin concentration ($p=0.027$) predicted an SCA pain adverse event. Seventy-six percent of the pain events occurred when the hemoglobin was less than or equal to 9.1 g/dL. Unexpectedly, fetal hemoglobin, Hb A and Hb S did not predict the occurrence of an SCA pain adverse event. White cell count ($p=0.002$), ALT ($p=0.012$), AST ($p=0.021$), and serum creatinine ($p=0.012$) independent of age, were significantly higher before SCA pain events. Total bilirubin, MCV, and LDH did not have any predictive or temporal relationship with SCA pain adverse events. With all significant parameters added to a single model, including treatment group and age at consent, only serum creatinine was significantly associated with an SCA pain event ($p=0.015$); WBC was suggestive but not significant ($p=0.093$).

These analyses were also conducted on the subset of subjects treated with hydroxyurea and phlebotomy. Higher creatinine ($p=0.034$), WBC ($p=0.007$), and LDH ($p=0.025$), and lower hemoglobin ($p=0.005$) predicted the occurrence of SCA pain events in this treatment group. With all significant parameters added to a single model, including treatment group and age at consent, only WBC was significantly associated with SCA pain events ($p=0.005$) in this treated population.

DISCUSSION

We have compared non-neurological AEs and SAEs of children with SCA who had a previous history of stroke, and were randomized to continue on blood transfusions with oral iron chelation or switched to hydroxyurea therapy with monthly phlebotomy for the management of secondary stroke prevention and iron overload. Special attention was paid to events commonly associated with SCA. This is the first prospective comparison of hydroxyurea and blood transfusions in children with SCA who meet criteria for chronic transfusions.

While the number of participants experiencing adverse events, both sickle cell-related and otherwise, was similar in the two treatment arms, more subjects who were on hydroxyurea with phlebotomy experienced SAEs and SCA-SAEs at higher annualized rates than did subjects on the standard arm; these differences were higher when the transfusion overlap period in the alternative arm was excluded. In particular, almost a fourth of subjects who were on hydroxyurea and phlebotomy experienced a sickle cell pain SAE, whereas less than 10% of the subjects on chronic transfusions and iron chelation had a serious sickle cell pain event. The difference between both treatment groups seen in the number of serious SCA pain episodes is not explained by poor adherence to hydroxyurea; the 6 month rolling average adherence computed for the time of the event was within acceptable limits (mean=88%), as evidenced by hydroxyurea pill counts. However, it should be noted that

previous adherence to monthly transfusions was a SWiTCH eligibility criterion, so only subjects who were known to be compliant with chronic transfusion therapy were enrolled.

Pain is the most common morbidity associated with sickle cell disease, and its frequency and severity vary with the sickle cell genotype and within individuals of the same genotype [16]. According to the Cooperative Study of Sickle Cell Disease (CSSCD), the seminal natural history study, children with hemoglobin SS ages 10-14 years and ages 15-19 experienced 0.69 and 0.91 pain episodes per person-year respectively [16]. Across treatments, our cohort appeared to have a similar incidence of pain episodes (0.90 events per person-year) to that seen in CSSCD. Whereas a painful event in CSSCD required a visit to a healthcare provider [17], for SWiTCH all pain events were collected, including, for example, historical self-reports of pain managed at home. Our analysis of predictors of SCA pain suggests that older age predicts the subjects' risk to have a sickle cell pain SAE. We did not find correlations with the alpha thalassemia status or beta globin haplotypes and pain. The study showed that an elevation of WBC predicted SCA pain events, especially in the hydroxyurea/phlebotomy group. White blood cells have been implicated in the vaso-occlusive event, possibly by contributing to leucocyte adhesion to the endothelium [18]. It is possible that the correlation of an elevated serum creatinine prior to a pain event may be related to dehydration; however, this information was not recorded.

There were no treatment group differences in the incidence of other SCA-related SAEs such as acute chest syndrome and infections, although the number of events may be too small to reach a meaningful conclusion. Acute chest syndrome is commonly defined as the presence of a new pulmonary infiltrate on chest x-ray, usually associated with fever and other respiratory symptoms [19]. The incidence of ACS, defined similarly for the CSSCD [20], was higher in patients with Hb SS ages 10-20 years (0.093 events per person-year) in CSSCD when compared to 0.05 events per person year across treatment groups in the SWiTCH study, confirming the beneficial effects of both hydroxyurea and chronic transfusions in preventing ACS.

Although chronic transfusions and hydroxyurea have been employed for years to offer palliation to patients, this is the first time that these treatments are compared in children with SCA, in the setting of a randomized clinical trial. Subjects receiving hydroxyurea and phlebotomy had similar numbers of sickle cell related events to those on chronic transfusions, although there were more serious events in the children who were switched to the hydroxyurea/phlebotomy arm. However, it is important to underscore that these children were stable and adherent to chronic transfusions on an average 7 years before switching to hydroxyurea and phlebotomies. In the past, a "rebound phenomenon" in pain symptoms was reported in sickle cell patients who stopped chronic transfusions [21].

Transfusions and chelation remain the best way to manage children with SCA, stroke, and iron overload. While SWiTCH demonstrated that transfusions and iron chelation remain the treatment of choice for secondary stroke prevention and management of iron overload, hydroxyurea may still be considered a treatment option under special circumstances (for example, religious reasons, inability to find compatible blood due to the presence of antibodies, poor compliance with chelation therapy), especially for those at lower risk for

stroke recurrence (minimal vasculopathy, higher hemoglobin on hydroxyurea). It is likely such patients will fare better with hydroxyurea than with no treatment at all, even if phlebotomy is not employed.

Although not advised based on the study results, if transfusions are abandoned for specific reasons and hydroxyurea started, clinicians should discuss with their patients that some may experience more frequent or severe pain episodes as compared to when they were receiving transfusions.

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APPENDIX

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Abbreviations

ACS	acute chest syndrome
AE	adverse event
ANC	absolute neutrophil count
Hb	hemoglobin
ITT	intention to treat

LIC	liver iron concentration
MTD	maximum tolerated dose
SAE	serious adverse event
SCA	sickle cell anemia

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Table I

Clinical Characteristics of ITT Participants in SWiTH

Parameter	Transfusion/Chelation N=66	Hydroxyurea/Phlebotomy N=67	P-value
Age at study entry (years)	13.3 ± 3.8	13.0 ± 4.0	0.733
Male	31 (47%)	41 (61%)	0.100
Hemoglobin SS	66 (100%)	66 (99%)	>0.999
Prior duration of transfusion therapy (years)	7.0 ± 3.6	7.4 ± 3.8	0.592
Hb at study entry (g/dL)	9.2 (8.6 - 9.7)	9.2 (8.5 - 9.6)	0.998
Hb at study exit (g/dL)	9.0 (8.7 - 9.6)	9.0 (8.4 - 9.6)	0.934
% Hb S at exit	32.3 (25.0 - 38.3)	64.1 (52.6 - 76.4)	<0.001
% Hb F at exit	1.3 (0.8 - 2.7)	19.5 (10.0 - 24.3)	<0.001
% Hb A at exit	63.6 (56.4 - 69.1)	1.7 (0.0 - 31.4)	<0.001
ANC at study entry	7.4 (6.2- 9.2)	7.1 (5.5- 10.2)	0.519
ANC at study exit	7.8 (6.5- 10.0)	3.8 (2.6- 5.5)	<0.001

Age and prior transfusion history at baseline are expressed as mean ± standard deviation, with treatment group differences assessed via analysis of variance. Laboratory parameters are expressed as median (interquartile range), with treatment group differences assessed via Wilcoxon rank sum. Categorical values are summarized as Count (%), with treatment group differences assessed via Chi-squared tests for gender and Fisher's exact test for sickle cell genotype.

All laboratory differences at study exit were expected based on the hematological effects of hydroxyurea.

ANC= absolute neutrophil count; Hb=Hemoglobin.

Table II

Summary of Counts and Percent of Subjects Experiencing at Least 1 Non-Neurological Adverse Event by Treatment Arm

	Transfusion/Chelation (N=66)		Hydroxyurea/Phlebotomy (N=67)		
Clinical Events	n (%)	Events	n (%)	Events	P-value
AEs	64 (97.0%)	550	64 (95.5%)	703	>0.999
SCA-related AEs	44 (66.7%)	171	46 (68.7%)	252	0.854
SCA pain	29 (43.9%)	82	38 (56.7%)	152	0.167
Infections and infestations ¹	31 (47.0%)	66	39 (58.2%)	92	0.226
Gastrointestinal disorder ¹	23 (34.8%)	41	27 (40.3%)	55	0.592
Fever	21 (31.8%)	39	23 (34.3%)	34	0.854
Musculoskeletal disorder (not attributed to SCA)	13 (19.7%)	23	15 (22.4%)	21	0.832
Immune system disorder ¹	8 (12.1%)	10	1 (1.5%)	1	0.017
Cholelithiasis	4 (6.1%)	4	3 (4.5%)	4	0.718
Cholecystitis	1 (1.5%)	1	2 (3.0%)	2	>0.999
Asthma	4 (6.1%)	5	3 (4.5%)	4	0.718
Acute chest syndrome	4 (6.1%)	4	7 (10.4%)	9	0.531
Renal or urinary disorder ¹	3 (4.5%)	4	2 (3.0%)	3	0.680
Priapism	1 (1.5%)	1	2 (3.0%)	5	>0.999
Catheter related complication	2 (3.0%)	2	3 (4.5%)	3	>0.999
Cardiac disorder ¹	1 (1.5%)	1	1 (1.5%)	1	>0.999
Lab AEs					
Hyperbilirubinemia ²	18 (27.3%)	49	9 (13.4%)	22	0.055
ALT increase	14 (21.2%)	36	15 (22.4%)	25	>0.999
AST increase	10 (15.2%)	18	14 (20.9%)	23	0.500
Serum creatinine increase	3 (4.5%)	6	6 (9.0%)	7	0.492
Thrombocytopenia	1 (1.5%)	5	7 (10.4%)	9	0.062
Reticulocytopenia	3 (4.5%)	3	21 (31.3%)	30	0.001
Neutropenia	1 (1.5%)	1	10 (14.9%)	13	0.009
Anemia ³	3 (4.5%)	3	20 (29.9%)	39	0.001

The n and % are based on subjects experiencing at least 1 event in the specified category. P-values are based on the Fisher's Exact test comparing numbers of subjects. Events column reflect counts of events.

¹ The following categories reflect system organ classes: Gastrointestinal disorders included nausea, vomiting, abdominal pain, diarrhea, and others. Musculoskeletal disorders included pain in extremities, arthralgia, back pain, musculoskeletal pain, and others. Renal and urinary disorders included dysuria, hematuria, renal papillary necrosis, and urinary retention. Cardiac disorders included palpitation and right ventricular failure.

² Hyperbilirubinemia was considered an AE if the total bilirubin was ≥ 5 mg/dL (grade 2 or higher grade according to the CTCAE, version 3.0, Guidelines).

³ Anemia was considered an AE if there was a reduction in hemoglobin concentration by at least 30% from the previous baseline level, or a reduction by at least 20% accompanied by an acute increase in spleen size. Hemoglobin level less than 7 g/dL was considered grade 2 or higher grade according to the CTCAE, version 3.0. Guidelines.

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Table III

Summary of Counts and Percent of Subjects and of Annualized Rates of Select Non-neurological, Serious Adverse Events by Treatment Arm

	Transfusion/Chelation (N =66) Person years of exposure=136.0			Hydroxyurea/Phlebotomy (N=67) Person years of exposure=124.3			P-value ¹
	n (%)	Events	Event Rate	n (%)	Events	Event Rate	
All SAEs	12 (18.2%)	26	0.19	26 (38.8%)	55	0.44	0.012
SCA-SAEs	7 (10.6%)	13	0.10	22 (32.8%)	48	0.38	0.003
SCA pain SAEs	5 (7.6%)	7	0.05	16 (23.9%)	27	0.21	0.016
Acute chest syndrome SAEs	3 (4.5%)	3	0.02	1 (1.5%)	2	0.02	0.365
Infections and Infestations SAEs	2 (3.0%)	3	0.02	7 (10.4%)	9	0.07	0.165
Splenic sequestration SAEs	0	0	0	0	0	0	>0.999

This table reflects a select subset of non-neurological *serious* adverse events known to be associated with SCA. Counts are numbers of subjects experiencing at least one event in the specified category. Event rates are number of events in the designated category per person year of exposure. The events reported for the Hydroxyurea/Phlebotomy arm include those that occurred during the overlap period.

¹ P-value based on a Fisher's Exact comparing numbers of subjects.

Table IV

Annualized Rates of Non-Neurological Events Categories in the Standard Arm and the Alternative Arm (Overall, Overlap, and Post-Overlap Periods)

	Transfusion/ Chelation N=66 Ann. Rate (95% CI)	Hydroxyurea/Phlebotomy Overall N=67 Ann. Rate (95% CI) [RR (95% CI)] P-value^I	HU/Phlebotomy Overlap N=67 Ann. Rate (95% CI) [RR (95% CI)] P-value^I	HU/Phlebotomy Post- Overlap N=60 Ann. Rate (95%CI) [RR (95% CI)] P- value^I
AEs	4.05 (3.32, 4.94)	5.65 (4.74, 6.73) [1.4 (1.07, 1.82)] 0.014	4.51 (3.34, 6.08) [1.11 (0.79, 1.57)] 0.543	5.79 (4.71, 7.12) [1.43 (1.08, 1.89)] 0.012
SCA-AEs	1.26 (0.90, 1.76)	2.02 (1.53, 2.66) [1.60 (1.04, 2.46)] 0.034	1.38 (0.82, 2.3) [1.09 (0.61, 1.96)] 0.772	2.02 (1.45, 2.82) [1.60 (1.01, 2.54)] 0.044
SAEs	0.19 (0.12, 0.32)	0.44 (0.31, 0.62) [2.27 (1.24, 4.17)] 0.008	0.19 (0.09, 0.41) [0.98 (0.41, 2.36)] 0.972	0.42 (0.28, 0.63) [2.18 (1.17, 4.06)] 0.015
SCA-SAEs	0.10 (0.05, 0.18)	0.38 (0.27, 0.53) [3.95 (1.92, 8.12)] <0.001	0.11 (0.05, 0.24) [1.13 (0.45, 2.84)] 0.803	0.38 (0.26, 0.56) [3.96 (1.98, 7.92)] <0.001
SCA Pain	0.60 (0.40, 0.92)	1.22 (0.89, 1.66) [2.01 (1.19, 3.40)] p=0.009	0.76 (0.42, 1.35) [1.25 (0.64, 2.44)] P=0.517	1.25 (0.87, 1.80) [2.07 (1.21, 3.54)] p=0.008
SCA Pain SAEs	0.05 (0.03, 0.10)	0.21 (0.15, 0.30) [4.06 (1.86, 8.87)] <0.001	0.08 (0.04, 0.17) [1.57 (0.63, 3.89)] 0.333	0.2 (0.13, 0.31) [3.92 (1.85, 8.32)] <0.001

Ann=Annualized; SCA=sickle cell anemia related.

^I Comparisons are to Tx/Chelation rates. Risk Ratios, 95% CIs, and P-values are estimated using a Poisson regression predicting AE count and including the main effect of treatment group. Over-dispersion was accounted for by rescaling the parameter estimate standard errors using the square root of the deviance divided by the degrees of freedom.