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Real-Life Experience with Hydroxyurea in Patients with Sickle Cell Disease: Results from the Prospective ESCORT-HU Cohort Study

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The data that support the findings of this study are available from the corresponding author.

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Ethic approval statement

An independent Ethics Committee approved the study in each country.

Patient consent statement

Oral or written informed consent was obtained for each patient according to the local rules for non-interventional studies.

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Not applicable.

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Abstract

Several controlled studies have evidenced good efficacy and short- and mid-term safety profiles for hydroxyurea (HU), which has become the cornerstone for prevention of sickle-cell disease (SCD)-related vaso-occlusive crises. However, there are few large-scale reports on its long-term use and certain caregivers and patients have concerns about its safety. Following the licensing of HU in Europe for children and adults with severe forms of SCD, ESCORT-HU was designed as a Phase IV observational cohort study. It included 1,906 participants, of whom 55% were adults. The most common hemoglobin (Hb) genotypes were HbSS (84.7%) and HbSβ+ (7.0%). The median duration of follow-up was 45 months, for a total of 7,309 patient-years of observation. The dose of HU after one year was 20.6 mg/kg/d for children and 16.3 mg/kg/d for adults. There was a statistically significant decrease in the number of vaso-occlusive episodes lasting > 48 hours, acute chest syndrome episodes, hospitalizations, and the percentage of patients requiring blood transfusions within the first 12 months relative to the year before enrolment. Neutropenia and thrombocytopenia were the most commonly reported adverse effects. No new HU toxicity was identified. Overall, 125 pregnancies were reported in 101 women and no malformations were observed in the neonates. There were 12 pregnancies for partners of male patients treated with HU. One case of fatal myelodysplastic syndrome was reported, for which a causal association with HU could not be excluded. This cohort study of patients with SCD highlights the positive benefit-to-risk ratio of HU in children and adults.

Keywords: hydroxyurea, effectiveness, safety, sickle cell.

INTRODUCTION

Background

Sickle-cell disease (SCD) is among the most frequently occurring monogenic diseases, characterized by the presence of abnormal hemoglobin S (HbS), either in a homozygous form (HbSS), or combined with another hemoglobin variant (most often Hemoglobin C or β-thalassemia).[1] In total, 40,000 SCD patients are estimated to be living in Europe.[2]

Hydroxyurea (HU) is a cornerstone for the prevention of vaso-occlusive crises (VOCs), the most frequent complication in SCD patients. The rationale for using this drug stems from findings that it increases fetal hemoglobin (HbF) levels, which interrupts elongation of deoxy-HbS polymers. Furthermore, HU decreases blood cells adhesion to the vascular endothelium and improves vascular tone.[3-5]

Although the clinical efficacy of HU in preventing pain has been demonstrated,[6-8] and its ability to increase life expectancy suggested,[9,10] many publications continue to report low/poor adherence to HU,[11,12] associated with a poor quality of life and school absenteeism.[13-15] Reluctance to use HU may be partially related to fears about potential side effects of this medication, especially in terms of fertility and carcinogenicity.[16] As malignancies are rare events, safety assessment requires very large-scale studies covering long periods of follow-up. Previous studies, based on the observation of cohorts of up to 150 patients, with a very long follow-up for two of them, have provided reassuring data but studies enrolling more than 1,000 patients with long periods of follow-up are still needed.[9,10]

The European Medicines Agency (EMA) gave marketing authorization for HU in 2007 for children older than two years, adolescents, and adults with SCD. The drug was indicated for the prevention of recurrent painful VOC crises, including acute chest syndrome (ACS). Asymptomatic patients were not planned to be included. Accordingly, the EMA requested the initiation of a European, multicenter, prospective, non-interventional study over a 10-year period, with the goal of including enough patients with prolonged HU exposure in current clinical practice to better document adverse events that may occur at a low frequency, with special attention to oncogenic risk. The Sickle Cell Disease Cohort–Hydroxyurea (ESCORT-HU) study was initiated upon this request and designed as a Phase IV, multicentric, cohort study.

The main objective was to refine the safety profile of HU and identify unexpected toxicity, especially after long-term treatment.

METHODS

Study population

Enrolment in ESCORT-HU began on January 1, 2009, and ended on June 30, 2017. Patients were enrolled from France, Germany, Italy, and Greece, where the drug was first available.

Patients aged two years and over with symptomatic SCD who were eligible for treatment with HU were enrolled. According to the European marketing authorization and national guidelines in the four countries in 2009, there was no recommendation to enroll asymptomatic patients. An independent Ethics Committee approved the study in each country. Oral or written informed consent was obtained for each patient according to the local rules for non-interventional studies.

HU was given in the form of 100 and 1000 mg tablets. Approximately half of the patients of the total cohort had previously received HU given as capsules (500 mg). The company marketing HU as capsules had not requested marketing authorization for SCD in Europe. Hence, patients previously treated with this capsule formulation were secondarily switched to HU tablets and included in ESCORT-HU (non-naive patients). The other half of the patients enrolled in ESCORT-HU started their HU treatment with the tablets (naive patients).

The prescription of HU had to be given by a physician with experience in the management of HU. France, Germany, Italy, and Greece have designated reference centers with expert physicians, based on the number of patients with SCD they are following and their experience in their management.

The EMA recommended an initial dose of 15 mg/kg/d, and no systematic attempt to reach the maximum tolerated dose (MTD). An increase in the dose was indicated if there were recurrences of VOC.

Follow-up was strictly observational and the patients were not requested to attend additional visits beyond routine clinical practice (i.e., every 1 to 6 months). A minimum of 12 months of follow-up was required.

Variables

Data from the participants' medical records were collected via an electronic case report form (eCRF), synthesizing all medical information, including outside events prior to inclusion. Their SCD history was recorded at inclusion, including SCD complications over the prior year. At each visit, data on the occurrence of painful crises lasting > 48 hours with hospitalization, ACS, the number and duration of hospitalizations related to SCD, and the number of blood transfusions since the last visit were collected. The number of pregnancies and instances of fatherhood were also noted.

The initial complete blood count (CBC) was noted, with, if available, G_6PD testing and the α- and β-globin genotypes. The recommendation was to monitor the CBC every two months and the percentage of fetal hemoglobin (HbF) every six months. Blood tests could be performed on an outpatient basis and forwarded to the physician or performed on an in-patient basis.

Safety was assessed in the global population (naive and non-naive patients). Adverse events were defined as any treatment-emergent event occurring during follow-up which was not considered to be a typical manifestation of SCD. Causal relationship to HU was assessed by the investigators. Adverse events related to HU (at least possibly) were considered adverse reactions.

Neutropenia was defined as an absolute neutrophil count (ANC) < 2,000/mm^3 and thrombocytopenia as an absolute number of platelets < 150,000/mm^3.

Effectiveness was assessed in the global population (naive and non-naive patients) by comparing biological data (Hb level and % HbF) at baseline and clinical outcomes (VOC events, hospitalizations, and blood transfusions) in the previous year with those observed after 6 and 12 months of HU (tablet) treatment.

Clinical research associates contacted each study site on a regular basis in order to perform quality control visits to check the quality of the data entered in the eCRF and limit missing data. Missing data were not managed.

Study Size

The required sample size was estimated to be approximately 2,000 patients, considering a 20% sample of an overall estimated number of 20,000 SCD patients (at the time of writing the

protocol) in Europe and approximately 50% requiring HU. This allowed for an estimation of the frequency of events as low as 0.5%, with a precision of 0.3%.

Statistical Analysis

Descriptive statistics were used to summarize the distribution of continuous variables using means (± SD), medians, and ranges, and categorical variables using frequencies and percentages for each category of the variable. Confidence intervals for the annual rate of adverse events were estimated using the Poisson method.

Biological and clinical outcomes were compared using paired t-tests or Wilcoxon's signed rank tests for continuous variables and McNemar's test for binary variables.

All p-values were calculated from two-sided tests and p-values < 5% were considered statistically significant. All statistical analysis was performed using SAS® software v9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

From January 2009 to March 2019, 1,906 patients from four European countries were enrolled: 1,578 from France, 173 from Greece, 145 from Germany, and 10 from Italy. Three patients were secondarily excluded because they did not meet the inclusion criteria (they were not receiving the tablet formulation). Two patients withdrew their consent. Ten patients stopped the treatment (3 for cytopenia, 3 for neurological events, and 4 for lack of efficacy). Fifty-one patients (2.6%) were secondarily lost to follow-up.

Among the participants, 55% were adults and 55% were female. Most patients had SS (84.7%) and $S\beta^+$ (7.0%) globin genotypes. Ten percent had G_6PD deficiency according to laboratory results. Among the patients who were tested for alpha-globin gene defects (n = 361), 149 (41.5%) had one or two alpha gene deletions (Table 1). French legislation does not allow the recording of patient's ethnicity and this data was thus not collected.

Indications for HU

Seventy-four percent of patients were prescribed HU for VOC (53.0%) or ACS (21.4%) and had on average number of 2.9 crises (SD, 2.6) with hospitalization during the year before enrolment. Twenty-six percent of patients were treated for other non-VOC complications, although these indications were not included in the European authorization. Severe chronic anemia was the most frequent indication among non-VOC complications (11.0 %), followed by conditional transcranial Doppler velocities (4.7%), and other indications (overt cerebral vasculopathy, organopathy [*e.g.*, nephropathy, retinopathy, and pulmonary hypertension], priapism, contraindication to blood transfusion, and unreported indications) accounted for the remaining 10%.

Exposure to HU

The estimated mean daily dose of HU after one year was 20.6 mg/kg/d (SD, 4.9) for children (n = 775) and 16.3 mg/kg/d (SD, 5.2) for adults (n = 930). One thousand two hundred seventeen patients (565 children and 652 adults) had at least one ANC < 3.0 G/L during the study.

Forty-nine percent of the cohort was already receiving HU capsules before enrolment in the study. The total duration of HU treatment was 43.4 months (SD, 23.1) for naive patients and 123.7 months (SD, 62.7) for non-naive patients. In total there were 7,309 patient-years of observation.

Outcomes

Safety

Adverse reactions to HU are summarized in Table 2. As expected, peripheral blood cytopenia, mainly neutropenia and thrombocytopenia, were the most common events. These reactions were generally mild or moderate in intensity and resolved rapidly with permanent or temporary dose reduction, but three patients dropped out of the study, one for pancytopenia and two for thrombocytopenia. No infection was reported during the neutropenic episodes. There was a statistically significant higher risk for neutropenia in children than adults (risk ratio [95%CI]: 1.92 [1.33, 2.77]), and a trend for a higher risk of thrombocytopenia. Aggravation of the underlying anemia was rare, with a statistically higher risk in adults than children (risk ratio: 2.6 [1.4, 4.8]), as well as in patients with renal impairment at enrolment relative to those without (risk ratio: 4.25 [2.52, 7.17]). Approximately one third of anemia aggravation episodes were reported alongside other types of cytopenia, whereas approximately two-thirds were

isolated episodes in which the role of HU was potentially confounded by other possible or undocumented etiologies (e.g., infection, coincident painful crisis, low baseline Hb level, or folate or cobalamin deficit), as the reticulocyte count was not systematically documented.

Skin toxicities were the second most reported adverse reaction, predominantly in adults, being mostly dry skin and nail pigmentation.

Other commonly reported reactions consisted of mostly self-reported gastrointestinal (nausea, abdominal pain), nervous system (dizziness, headache), and general (fatigue) disorders, predominantly in adults. Three patients dropped out for neurological symptoms (one for headache, one for memory problems, and one for stroke).

Thirty-three deaths were reported in the study. One child died in the days following a hematopoietic stem cell transplant. Out of the 32 adults who died, no relation with HU was suspected in 31 cases; one patient had a car accident; one patient died during a severe VOC, 2 during an ACS, 2 patients had pulmonary embolism; 18 patients had an acute organ failure (heart failure, stroke, liver failure, renal failure) on an underlying chronic organ damage. No cause for death was reported for 7 patients, 6 of them had regular follow-up but died either at home or in a different hospital than their reference center, and one died in another country one year after having stopped HU. One fatal hematological malignancy (myelodysplastic syndrome with an excess of blasts-1, WHO classification 2016)[17] was reported for which a causal association with long-term HU use could not be excluded. No other adverse reactions were associated with a fatal outcome.

Overall, 125 pregnancies were reported for 101 women: 110 with exposure to HU (generally during the first trimester) and 15 without HU exposure (HU stopped at least 15 days before conception), despite the recommendation to discontinue HU 3 to 6 months before conception. The pregnancy outcomes included live births (n = 77), elective termination (n = 18), spontaneous abortion (n = 17), or ongoing pregnancy (n = 9). Other reported outcomes were anembryonic gestation (n = 1), ectopic pregnancy (n = 1), and termination for medical reasons (n = 2). No malformations among the neonates or maternal deaths were reported. There were 12 pregnancies of partners of male patients treated with HU. The outcomes were 10 live births (83%) and two miscarriages (17%).

Effectiveness

Comparison between the year before the initiation of treatment with HU in tablets and the first year of treatment showed a reduction in the number of painful crises lasting > 48 hours (-40% in children and -50% in adults), episodes of ACS (-68% in children and -57% in adults), and hospitalizations (-44% in children and -45% in adults) and the percentage of patients requiring blood transfusion decreased by 50% (Table 3). Nevertheless, 4 patients dropped out of the study for recurrent VOC.

Changes in Hb level, percentage of HbF, neutrophil counts, and mean corpuscular volume (MCV) for children and adults after 6, 12, and 24 months of treatment with HU tablets are shown in Figure 1. As expected, Hb levels significantly increased ($p < 0.01$), as did the percentage of HbF ($p < 0.01$). There was a significant increase in MCV ($p < 0.001$) and a significant decrease in absolute neutrophil counts ($p < 0.001$).

DISCUSSION

ESCORT-HU is a phase IV study that enrolled nearly 2,000 patients with SCD and has totalized more than 7,000 patient-years of observation, thus providing new and extensive data about the long-term safety of HU.

The pivotal controlled studies demonstrating the efficacy of HU were based on periods of observation of up to 30 months and the treatment arms included 60 to 150 patients.[6-8, 18,19] Prospective long-term follow-up studies enrolled less than 200 patients.[9,10, 20, 21] However, there was still a need for prospective long-term, large-scale studies to assess the long-term tolerance of HU, so studies performed in real life are of particular interest, as they provide outcomes observed without the incentive measures to attend clinical visits and perform control examinations associated with clinical trials.[22, 23] The most important finding was that no new risks were identified relative to previously acquired knowledge based on shorter studies[24,25]. Mild to moderate myelosuppression, involving mainly neutropenia and, to a lesser extent, thrombopenia, was the most common adverse reaction and was not associated with any clinical adverse events. Such good tolerance was observed despite the fact that the number of clinical and biological visits was low, as the median annual number of visits per patient was 0.5. Those results were observed with doses of approximately 20 mg/kg/d (SD, 5) in children and 17 mg/kg/d (SD, 5) in adults, consistent with other European studies, but lower than those used in

the TWiTCH study, for example.[18,20,21] The EMA recommended an initial dose of 15 mg/kg/d and no systematic attempt to reach the MTD, most probably because of uncertainties about very long-term effects. Instead, the minimal clinically effective dose (meaning the lowest dose providing the expected clinical benefit) was targeted. However, the initial dose was progressively increased in 44% of patients during the follow-up because of recurrent VOC events.

Major concerns about mid- and long-term toxicity concerned carcinogenicity and male infertility. The carcinogenic risk appears to be very low, as we observed only one case of fatal myelodysplastic syndrome for which a causal association with long-term HU use could not be excluded. There have been very few cases of myelodysplastic syndrome or acute leukemia after HU administration to patients with SCD.[26] Furthermore, *in vitro* assays and rodent studies have not shown mutagenic activity[27] and no case has been reported in the longest follow-up cohorts[9,10], suggesting that these events could be simply related to SCD or aging of the population.[28]

A significant number of pregnancies and instances of fatherhood were observed, with no critical issues. No abnormalities were observed in the babies, even though most mothers were exposed to HU treatment at the beginning of pregnancy, despite the recommendation given to patients. This finding is consistent with the absence of teratogenic effects of HU in previous reports of human pregnancies in which mothers were exposed to therapeutic doses of HU.[29,30] Interestingly, there was a lower number of instances of fatherhood than motherhood. We cannot exclude that male partner pregnancies were underreported, but as our study was prospective and aimed to record this event, the rate of underreporting should have been low. The low number of instances of fatherhood could be explained by the negative impact of SCD on fertility shown for human males, as a high proportion of semen analyses in patients with SCD not treated with HU show alterations in sperm parameters.[31-33] HU most likely decreases spermatogenesis, but additional studies are needed to assess whether this effect is reversible.[34,35] Preliminary evidence suggests that the effect of HU on spermatogenesis and sperm quality may be reversed when HU is stopped.[36]

In terms of effectiveness, the study suggests a consistent clinical benefit and stable improvement of Hb and HbF levels. There was a statistically significant decrease in the number of VOC

episodes lasting > 48 hours, episodes of ACS, number of hospitalizations and days of hospitalization, and the percentage of patients requiring blood transfusions within the first 12 months relative to the year before enrolment. These data observed in a real-life setting are consistent with those reported in controlled trials.

In contrast to the NIH and British recommendations, the European countries collaborating in ESCORT-HU still recommend not treating asymptomatic children or trying to reach the MTD.[37,38]. It is possible that recently published data will modify this strategy. A trial randomized HU at a fixed dose (approximately 20 mg/kg/d) with dose escalation (approximately 30 mg/kg/d) in Sub-Saharan children of approximately five years of age. Total follow-up was 18 months. Children in the dose-escalation group had fewer sickle cell–related adverse events and similar dose-limiting toxic effects as those observed in the lower-dose group. [39]

Our study had some limitations. Investigators were asked to prospectively enroll consecutive patients who met the eligibility criteria to limit selection bias in the recruitment of study patients, but as patients already treated with HU were also included, prevalent user bias could not be avoided. Investigational sites of the ESCORT-HU study were reference centers for SCD, thus limiting potential information/detection bias. No adherence study was performed given the very high number of patients enrolled. Another limitation was that the imputation of adverse events to HU was made by the investigating clinicians and not pharmacology experts. Finally, ESCORT-HU was funded by a pharmaceutical company, which participated in the design and conduct of the study and funded the collection of the data. Nevertheless, the principal investigators analyzed the data and wrote the manuscript.

Our study, performed in real-life settings, provides evidence of a clear clinical benefit, along with good tolerance, despite infrequent clinical and biological follow-up. It supports, therefore, the use of HU in low-income countries in which patients do not have easy access to laboratory facilities. Several studies conducted in Africa have confirmed the high efficacy and good tolerance of HU in children.[19,39-42] Given the reduced availability of pain killers, antibiotics, safe transfusion, and stroke prevention by transcranial Doppler in many African countries, a number of authors recommend systematic treatment of all infants after the age of one year.[43] However, HU in Africa is rarely utilized due to lack of availability and excessive cost.

In conclusion, the results of ESCORT-HU emphasize the positive benefit-to-risk ratio for children and adults with SCD in real life. HU is not a cure and families and patients may feel discouraged if recurrent VOC events still occur. However, the current opportunities to cure SCD, in the form of hematopoietic stem-cell transplantation and gene therapy, are in many cases inaccessible and entail the risks related to myeloablation. The addition of new emerging drugs (alone or in combination with HU) offers hope to reducing remaining painful episodes.[44] However, HU still remains currently the drug for SCD with the best risk/benefit profile. Finally, our data strongly support strategies that make it possible to offer HU to low-resource countries. Additionally, in 2020, ESCORT HU extension study has been initiated in the four countries participating in the first study. This extension should provide even more information regarding some risks such as secondary malignancies, leg ulcers, fertility and pregnancies.

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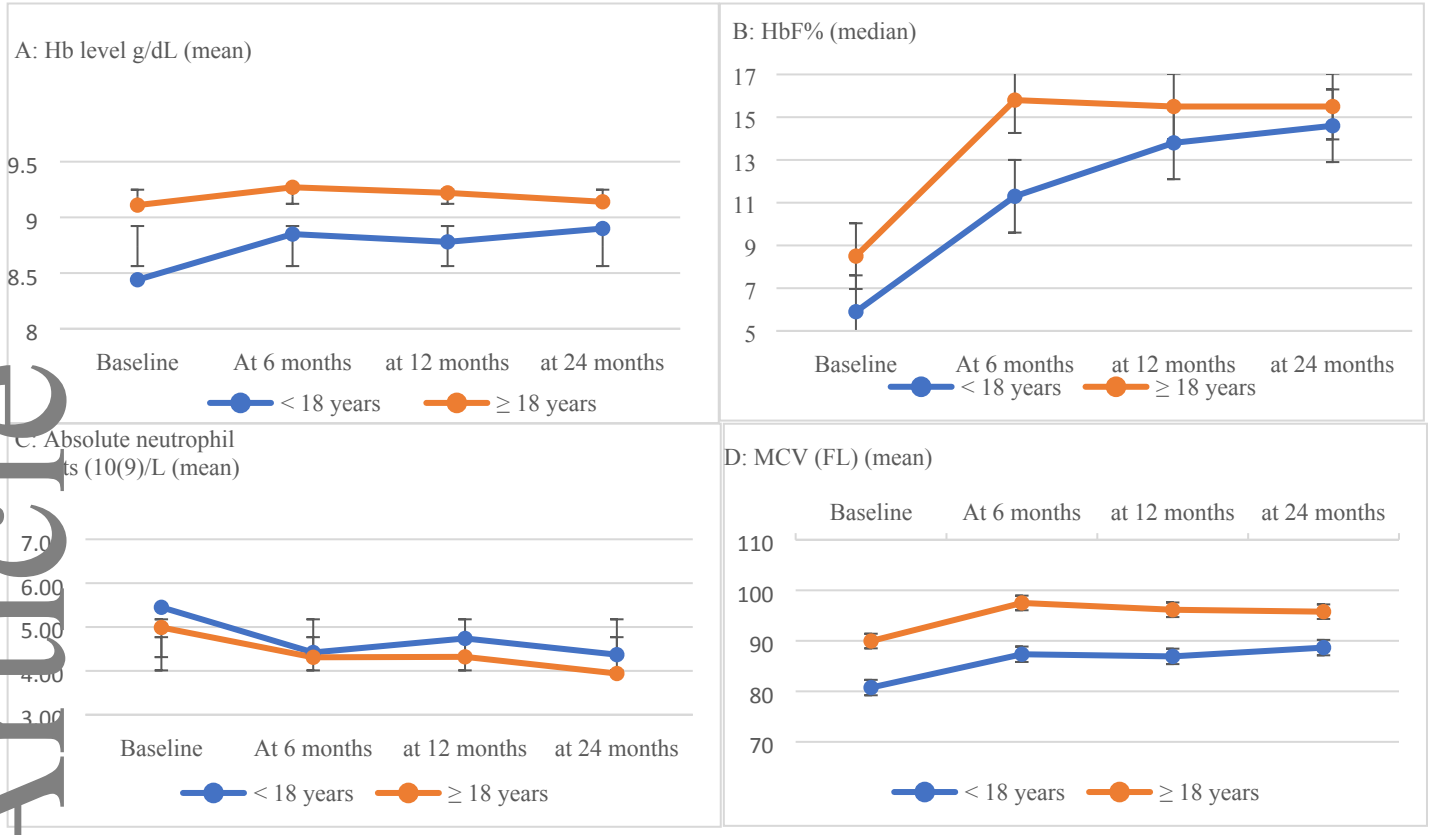

Figure 1. Outcome of (A) Hb level, (B) percentage of HbF, (C) neutrophil counts, (D) MCV for children and adults after 6, 12 and 24 months of treatment with HU tablets.

Hb: hemoglobin; HU: Hydroxyurea; MCV: mean corpuscular volume.

Table 1. Baseline demographic and genotype characteristics

	Age < 18 years (n=849)	**Age ≥ 18 years (n=1,054)**	**Total (n=1,903)[a]**
Sex, no. (%)			
Male	441 (51.9%)	411 (39.0%)	852 (44.8%)
Female	408 (48.1%)	643 (61.0%)	1051 (55.2%)
Age, mean (SD), years	9.1 (4.5)	35.2 (11.5)	23.6 (15.8)
Age, median (range), years	8.9 (0.8, 18.0)	33.5 (18.9, 70.4)	21.4 (0.8, 70.4)
Patients with determined β-globin genotype, No.	836	1,034	1,870
β-globin genotype, No. (%)			
SS	767 (91.7%)	816 (78.9%)	1,583 (84.7%)
SC	12 (1.4%)	26 (2.5%)	38 (2.0%)
$Sβ^0$	31 (3.7%)	83 (8.0%)	114 (6.1%)
$Sβ^+$	25 (3.0%)	105 (10.2%)	130 (7.0%)
SD	1 (0.1%)	2 (0.2%)	3 (0.2%)

[a] 3 patients were excluded from analysis as they did not meet the inclusion criteria (not treated with the tablet formulation

Table 2 Adverse reactions with rates > 1 per 100 patient-years collected in the 1,903 patients during the study (7,309.5 patient-years) by age group.

Adverse reaction[a]	Age < 18 years (n= 849, 3,078.2 patient-years)			Age ≥ 18 years (n=1,054, 4,231.4 patient-years)		
	No. of reactions	No. of patients	rate per 100 patient-years [95%CI]	No. of reactions	No. of patients	rate per 100 patient-years [95%CI]
At least one adverse reaction	275	150	8.9 [7.9, 10.1]	712	347	16.8 [15.6, 18.1]
Blood and lymphatic system disorders	196	113	6.4 [5.5, 7.3]	213	130	5.0 [4.4, 5.8]
Neutropenia	103	68	3.3 [2.7, 4.1]	52	44	1.2 [0.9, 1.6]
Thrombocytopenia	61	49	2.0 [1.5, 2.5]	65	51	1.5 [1.2, 2.0]
Anemia	13	13	0.4 [0.2, 0.7]	48	42	1.1 [0.8, 1.5]
Skin and subcutaneous tissue disorders	41	37	1.3 [1.0, 1.8]	290	178	6.9 [6.1, 7.7]
Dry skin	13	13	0.4 [0.2, 0.7]	109	107	2.6 [2.1, 3.1]
Alopecia	3	3	0.1 [0.0, 0.3]	38	36	0.9 [0.6, 1.2]
Leg ulcer	1	1	0.0 [-]	45	32	1.1 [0.8, 1.4]
Nail pigmentation	6	6	0.2 [0.1, 0.4]	22	21	0.5 [0.3, 0.8]
Nail discolouration	1	1	0.0 [-]	20	20	0.5 [0.3, 0.7]
Gastrointestinal disorders	13	13	0.4 [0.2, 0.7]	46	39	1.1 [0.8, 1.5]
Nervous system disorders	12	9	0.4 [0.3, 0.7]	58	43	1.4 [1.0, 1.8]
Headache	7	7	0.2 [0.1, 0.5]	29	27	0.7 [0.5, 1.0]
Dizziness	5	4	0.2 [0.1, 0.4]	22	20	0.5 [0.3, 0.8]
General disorders and administration site conditions	1	1	0.0 [-]	24	23	0.6 [0.4, 0.8]
Weight increase	1	1	0.0 [-]	27	27	0.6 [0.4, 0.9]
Death		1		32		33

[a] Adverse events that occurred in participants are included and presented by their preferred terms according to the Medical Dictionary for Regulatory Activities version 19.1.
[b] Neutropenia was defined as absolute neutrophil count < 2,000/mm^3.
[c] Thrombocytopenia was defined as absolute number of platelets < 150,000/ mm^3.

Table 3. Comparisons of clinical and biological parameters at enrolment and after one year of HU treatment by age group.

	Age < 18 years (n = 849)				Age ≥18 years (n= 1,054)			
	n	during the previous year	1 year after the initiation of HU tablets	Change Pre-post (p-value)	n	during the previous year	1 year after the initiation of HU tablets	Change Pre-post (p-value)
No. of VOC, mean (SD)	682	1.6 (2.1)	0.9 (1.6)	-50% (< 0.05)	907	1.8 (2.6)	0.9 (1.9)	-38% (< 0.05)
No. of ACS, mean (SD)	708	0.3 (0.7)	0.1 (0.3)	-67% (< 0.05)	940	0.3 (0.6)	0.1 (0.4)	-67% (< 0.05)
No of Hospitalizations, mean (SD)	681	1.7 (1.8)	0.93 (1.5)	-46% (< 0.05)	930	1.3 (1.8)	0.7 (1.3)	-44% (< 0.05)
No of days of hospitalization for SCD, mean (SD)	628	9.7 (12.1)	5.5 (10.1)	-46% (< 0.05)	833	8.1 (13.4)	4.4 (10.8)	-43% (< 0.05)
No of patients (%) with at least one blood transfusion	810	369 (45.6)	199 (24.6)	-21% (< 0.001)	1024	400 (39.1)	177 (17.3)	-21.8% (< 0.001)

Abbreviations: HU: hydroxyurea; SCD: sickle cell disease; VOC: vaso-occlusive crises; ACS: acute chest syndrome.