| Title | **ESCORT-HU: European Sickle Cell Disease Cohort - Hydroxyurea Clinical study report** |
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| **Protocol identification number** | ADD_12304_ESCORT-HU |
| **Date and version of the report** | Final: 16-Dec-2019 |
| **Study registration number** | NCT02516579 |
| **ENCEPP registration number** | SDPP 10565 |
| **Investigational product** | Siklos® |
| **Indication** | Sickle Cell Disease |
| **Marketing authorisation holder** | Addmedica |
| **Countries of study population** | France, Germany, Greece, Italy |
| **Sponsor** | ADDMEDICA<br>37 rue de Caumartin, F-75009 PARIS |
| **Rational and background** | The role of HU in the prevention of painful crises and in decreasing hospitalisations and blood transfusion needs in SCD patients is well-established. However, long-term safety data are limited, particularly in some specific subgroups and their assessment was requested by the European Medicines Agency as part of Siklos® Risk Management Plan. |
| **Research question and objectives** | **Primary objective**<br>The objective of this cohort study was to collect information on long-term safety of Siklos® (hydroxycarbamide or hydroxyurea [HU]) when used in current practice for the prevention or treatment of symptomatic complications in patients with Sickle Cell Disease. The following information was collected:<br>• Myelosuppression (requiring permanent or temporary discontinuation of therapy) secondary to HU-induced myelotoxicity<br>• Malignancies, skin ulceration and impaired postnatal development (growth)<br>• Amenorrhea, fertility impairment.<br>Particular attention was given to special populations or circumstances: young patients , elderly patients, patients with underlying SCD-related hepatic or renal impairment, pregnancy (and its outcome), concomitant use of HU and specific therapies (HIV drugs, other myelosuppressive agents, radiation therapy, live vaccines).<br>**Secondary objectives**<br>The secondary objectives were to evaluate the overall mortality and survival time as well as the occurrence of SCD events (painful crises, infections, acute chest syndrome, stroke, acute splenic sequestration). |
| **Study design** | This was a multicentre, prospective, non-interventional cohort study in patients with SCD treated with Siklos® and followed-up for up to 10 years. |

**Subjects and study size, dropouts**

The estimated sample size was 2000 patients in order to allow estimation of frequencies of events as low as 0.5% with a precision of 0.3%. A total of 1906 patients were included in the study. At least one follow-up visit was available for 1854 patients and most of patients were followed-up for at least 24 months (82.8%).

**Variables and data sources**

Occurrence of events of interest (myelosuppressions, malignancies, skin ulcerations, amenorrhea and related and non-related SCD events including serious events and death) as well as data on growth development, fertility status and pregnancy were collected from patients' medical file.

**Results**

The first patient was enrolled on 21-Jan-2009 and the last patient was enrolled on 27-Jun-2017. The last visit of the last patient was on 20-Mar-2019. A total of 1906 patients were included in the study in 4 European countries.

**Table 1. Number of patients included per country**

| | | Number of patients by centres | | | | | Number of patients included by country (N=1906) |
|---|---|---|---|---|---|---|---|
| **Country** | **Number of centres** | **<10** | **]10-20[** | **]20-50[** | **]50-100[** | **>100** | |
| France | 53 | 15 | 15 | 15 | 7 | 1 | 1578 |
| Greece | 1 | - | - | - | - | 1 | 173 |
| Germany | 5 | 2 | 1 | 1 | 1 | - | 145 |
| Italy | 3 | 3 | - | - | - | - | 10 |

**Table 2. Demographics of the cohort**

| | | [2-10] years (N=464) | ]10-18[ years (N=355) | ≥18 years (N=1054) | Total (N=1903) |
|---|---|---|---|---|---|
| Sex | n | 464 | 355 | 1054 | 1903 |
| | Male | 242 (52.2%) | 183 (51.5%) | 411 (39.0%) | 852 (44.8%) |
| | Female | 222 (47.8%) | 172 (48.5%) | 643 (61.0%) | 1051 (55.2%) |
| Age (years) | n | 464 | 355 | 1054 | 1903 |
| | Median | 6.1 | 13.3 | 33.5 | 21.4 |
| | Min - Max | 2.0 ; 9.9 | 10.0 ; 18.0 | 18.0 ; 70.4 | 0.8 ; 70.4 |

**Table 3 Genotype of the patients**

| | [2-10] years (N=464) | ]10-18[ years (N=355) | ≥18 years (N=1054) | Total (N=1903) |
|---|---|---|---|---|
| n | 456 | 351 | 1034 | 1870 |
| SS | 423 (92.8%) | 316 (90.0%) | 816 (78.9%) | 1583 (84.7%) |
| SC | 4 (0.9%) | 8 (2.3%) | 26 (2.5%) | 38 (2.0%) |
| Sβ0 | 18 (3.9%) | 13 (3.7%) | 83 (8.0%) | 114 (6.1%) |
| Sβ+ | 10 (2.2%) | 14 (4.0%) | 105 (10.2%) | 130 (7.0%) |
| SD | 1 (0.2%) | 0 (0.0%) | 2 (0.2%) | 3 (0.2%) |
| SO | 0 (0.0%) | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |

Demographic and genotypic characteristics of the patients included in this study are representative of the SCD population treated with Siklos® in the European participating countries. The median duration of participation in the study was 3.8 years. Almost half of the patients (48.7%) had already received a HU treatment other than Siklos® at enrolment, and for these patients, median exposure to HU treatment was 8.8 years.

The mean (± SD) dosage at Siklos® initiation is in line with the SmPC which recommends a starting dose of 15mg/kg/day for the overall population (15.36 ± 4.25mg/kg/day at enrolment in the subgroup of patient without previous HU treatment) but also for the specific subgroups including patients with renal impairment for whom the mean dosage was lower (11.2 ± 4.4mg/kg/day).

The main purpose of the study was to analyse the safety in terms of myelosuppression (requiring permanent or temporary discontinuation of therapy) secondary to HU-induced myelotoxicity, malignancies, skin ulceration. In line with the SmPC of Siklos, AEs with suspected relationship to Siklos® were predominantly blood and lymphatic disorders (409 events reported by 12.8% of the total population) and skin and subcutaneous disorders (331 events reported by 11.3% of the total population).

Within the 10 years of follow-up, 33 Deaths (23 women, 10 men) occurred (Mean age at death= 49 years old). The causes reported by investigators were:

- 70% related to the disease: Acute complications (Stroke, VOC, ACS, embolism) or chronic (renal, cardiac or hepatic impairment)
- 27% related to intercurrent condition: pulmonary embolism, epileptic seizure, cerebral haemorrhage
- 1 myelodysplastic syndrome possibly related to HU.

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| **Discussion and conclusion** | This study was an observational study and by nature, has bias due to investigator selection. However, as the participating sites accounted for nearly 99% of all reference centres in France, the characteristics of the investigators of the ESCORT-HU study were similar to the characteristics of the population of physicians initiating Siklos® and managing SCD patients. Quality control visits took place during the study in order to ensure quality of the data and limit missing data. However, despite all these measures, some biases inherent to a long-term follow-up study in current practice could not be avoided.<br><br>Overall, no major new safety signal was detected during the study. Non-SCD-related events reported in the study were in line with Siklos® SmPC.<br><br>The increased risk of myelosuppressive neutropenia in children compared to adults observed in this study was due to dose escalation to maximal tolerated dose more often used in children than in adults and adaptation to a body weight which varies significantly in pediatric population. Furthermore, the incidence of HU-related anaemia in this study might have been overestimated due to various confounding factors mainly represented by hemolytic crisis, splenic sequestration, vaso-occlusive crisis, folate and iron deficiencies, renal impairment, viral infection.<br><br>Other HU-related events including leg ulcers and malignancies require more information to determine the role of HU in the occurrence of these events and will be further studied in ESCORT-HU extension study.<br><br>In females, although outcomes of pregnancies during HU treatment are reassuring, it is highly recommended to avoid foetal exposure to HU. For women suffering from severe SCD symptoms who are required to continue HU, a strict monitoring of the mother and the foetus is necessary. Regarding male fertility, there is probably under-reporting of impairment, which is expected by the clinicians. But sperm cryopreservation must be encouraged before the beginning of HU or in young children re-evaluated after puberty. Female and male fertility will be further studied in ESCORT-HU extension study. |