CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208843Orig1s000

CLINICAL REVIEW(S)

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, M.D.
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	**208843 resubmission**
Applicant	Addmedica SAS
Date of Submission	06/30/2017
PDUFA Goal Date	12/30/2017
Proprietary Name	Siklos
Established or Proper Name	hydroxyurea
Dosage Form(s)	100 mg and 1000 mg tablets
Applicant Proposed Indication(s)/Population(s)	Pediatric patients To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises
Action or Recommended Action:	*Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	SIKLOS is an antimetabolite,indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older, with sickle cell anemia with recurrent moderate to severe painful crises.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Rachel Ershler, MD/Nicole Gormley, MD**
Statistical Review	**Yaping Wang, Ph.D./Yuan-Li Shen, D.Phil.**
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OPQ Review	**Mei Ou, Ph.D./Okpo Eradiri, Ph.D./Angelica Dorantes, Ph.D./Anamitro Banjeree, Ph.D.**
Microbiology Review	**N/A**
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OPDP	
OSI	
CDTL Review	**Nicole Gormley, M.D.**
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OSE/DRISK	
Other	

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Overview and General Instructions

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Sickle Cell Disease (SCD) is the most common inherited red blood cell (RBC) disorder. Worldwide, it is estimated that over 200,000 children affected with SCD are born every year, primarily in sub-Saharan Africa (180,000 births per year). Approximately 2000 children in the United States (US) are born with SCD each year, with a disease incidence of 1 in 2474 live births. The estimated prevalence of SCD in the US ranges from 70,000-140,000 [3]. In the US, the median survival for HbSS and HbSC disease is 58 and 66 years, respectively. SCD results from a single genetic point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of hemoglobin. This mutation leads to an abnormal form of hemoglobin, known as sickle hemoglobin (HbS). People who inherit two copies of the HbS mutation are homozygous (HbSS) and have the disease phenotype, whereas heterozygous carriers (HbAS) have sickle cell trait and do not exhibit clinical disease. The abnormal HbS results in deformed and fragile RBCs thathave a characteristic sickle shape and a reduced lifespan. The sickled RBCs occlude the microvascular circulation, which leads to tissue ischemia, infarctions and chronic hemolytic anemia.

SCD is characterized by heterogeneous disease manifestations and complications that worsen with age including acute vaso-occlussive crises (VOCs), chronic pain, chronic hemolytic anemia, recurrent infections, and neurologic complications. Additionally, vascular injury from chronic ischemia leads to multi-organ dysfunction and early mortality. In infants and children, SCD may cause poor nutritional status and delayed growth and puberty. VOCs are the most common acute manifestation of SCD and cause significant morbidity. Hydroxyurea and L-glutamine are the only pharmaceutical agents that are FDA approved for the treatment of sickle cell disease. However L-glutamine is not approved for pediatric patients less than 5 years of age. Therefore, there is a great need for novel and effective treatments in this patient.

Despite study of hydroxyurea in pediatric patients with SCD, no data has ever been submitted for an approval decision. Addmedica provided the results of a multicenter, prospective, non-interventional study of Siklos® in subjects ≥ 2 years of age with symptomatic SCD. The initial starting dose was 15 mg/kg/day, which was titrated by 5 mg/kg increments every 8 weeks to a maximum dose of 35 mg/kg/day. This study was supported by published literature which contained the results of 28 available randomized controlled trials and single arm trials in pediatric patients. After at least 6 months of treatment with Siklos® product, there was an increase from baseline in Hemoglobin F (8.01 ± 8.38%). The number of clinical events decreased in the 12 months after Siklos® initiation when compared to the 12 months prior to prior to treatment. The number of patients with ≥1 painful crisis in the preceding 12 months decreased from 83 (69.2%) at baseline to 51 (42.5%) at 12 months (120 evaluable patients). The number of patients experiencing at least one episode of acute chest syndrome decreased from 29 (23.6%) at baseline to 7 (5.7%) patients at 12 months (123 evaluable patients). The number of patients with at least 1 hospitalization related to SCD decreased from 83 (75.5%) at baseline to 46 (41.8%) at 12 months (110 evaluable patients). Decreases were also seen in the number of patients who received at least 1 transfusion.

No new safety issues were identified in the study for Siklos, although the database was limited. The safety profile was as expected for Siklos (hydroyxurea) a cytotoxic with infections, myelosuppression, gastrointestinal disturbance, headache, nervous system issues, fertility issues, potential for embryofetal harm and second malignancies. Hydroxyurea has been an approved product in the US for more than 50 years used for the treatment of malignancy and sickle cell disease primarily.

Some of the text above may also be found in the medical office and CDTL reviews.

This is a notable approval for the treatment of pediatric patients with sickle cell disease.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Sickle Cell Disease (SCD) is the most common inherited red blood cell (RBC) disorder. Approximately 2000 children in the United States are born with SCD each year, with a disease incidence of 1 in 2474 live births. SCD has many disease manifestations. Vascular injury from chronic ischemia leads to multi-organ dysfunction and early death.	SCD is a serious and life-threatening condition.
Current Treatment Options	• Hydroxyurea which is most commonly approved medication for the treatment of sickle cell crises is not approved for the pediatric population. It is used off-label. In 2017, L-glutamine was approved for pediatric patients aged 5 years and older.	Important to approve and label medications for pediatric use.
Benefit	• The clinical benefit of Siklos® in pediatric patients was determined by the efficacy results of Study ESCORT-HU, as well as the previous findings of efficacy of Droxia® in adult subjects with SCD (via extrapolation to pediatric patients). Efficacy was also supported by data from two published controlled studies with the same target indication as Siklos, three published controlled studies in pediatric patients with SCD, one long-term follow-up study of registries in Belgium and France, and 18 additional open-label, non-controlled studies. • ESCORT-HU was a multicenter, prospective, non-interventional study of Siklos® in subjects ≥ 2 years of age with symptomatic SCD. The initial starting dose was 15 mg/kg/day, which was titrated by 5 mg/kg increments every 8 weeks to a maximum dose of 35 mg/kg/day.	• Siklos® use resulted in an increase in hemoglobin F, which has been associated with improvements in clinical manifestations in patients with SCD. • Siklos® use was shown to demonstrate an improvement in several key sickle cell disease manifestations including painful crises, acute chest syndrome, number of hospitalizations, days of hospitalization, and number of patients requiring blood transfusions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• After at least 6 months of treatment with Siklos®, there was an increase from baseline in Hemoglobin F (8.01 ± 8.38%). • The number of clinical events decreased in the 12 months after Siklos® initiation when compared to the 12 months prior to treatment. • Siklos® use was shown to demonstrate an improvement in several key sickle cell disease manifestations including painful crises, acute chest syndrome, number of hospitalizations, days of hospitalization, and number of • The number of patients with ≥1 painful crisis in the preceding 12 months decreased from 83 (69.2%) at baseline to 51 (42.5%) at 12 months (120 evaluable patients). • The number of patients experiencing at least one episode of acute chest syndrome decreased from 29 (23.6%) at baseline to 7 (5.7%) patients at 12 months (123 evaluable patients). • The number of patients with at least 1 hospitalization related to SCD decreased from 83 (75.5%) at baseline to 46 (41.8%) at 12 months (110 evaluable patients). • Decreases were also seen in the number of patients who received at least 1 transfusion.	
Risk and Risk Management	• The safety population for Study ESCORT-HU included 405 pediatric subjects in the Global Safety Set. • The median duration of exposure to Siklos® was 18 months. • Serious adverse reactions (including both SCD-related events and non-SCD related events) were reported in 109 (26.9%) of subjects. • The most frequent non-SCD related events were bacterial infections (11.9%), neutropenia (11.1%), and viral infections (7.4%). • One death in a pediatric patient (unrelated to Siklos®treatment). • Prescribers should be aware of the risks of myelosuppression, the potential for secondary malignancies, embryo-fetal toxicity, cutaneous vasculitic toxicities, risks with concomitant use of antiretroviral drugs and live virus vaccines. The proposed labeling includes warnings and precautions	Younger children appear to have an increased risk of myelosuppression, particularly neutropenia, when compared to older children and adults. All pediatric patients should be monitored regularly for myelosuppression, particularly at the time of dose adjustments for increased body weight. It is recommended that the label contain a boxed warning for myelosuppression and malignancies. Additional warnings and precautions include embryo-fetal toxicity, cutaneous vasculitic toxicities, risks with concomitant use of antiretroviral drugs, and concomitant use with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	including recommended monitoring, and dose modifications. Safe use will require that both patients and healthcare providers are aware of these instructions.	live virus vaccines.

2. Background

Hydroxyurea has been approved since 1967 for treatment of malignancy.
Hydroxyurea has been approved since 1998 for the treatment of sickle cell disease for adult patients.

3. Product Quality

No remaining issues

4. Nonclinical Pharmacology/Toxicology

No remaining issues

5. Clinical Pharmacology

No remaining issues

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

See Benefit/risk.

8. Safety

No new safety issues were identified in this application.

9. Advisory Committee Meeting

N/A

10. Pediatrics

This is an application with pediatric data. See above.

11. Other Relevant Regulatory Issues

All resolved.

12. Labeling

Labeling is PLR and PLLR compliant.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Other Postmarketing Requirements and Commitments

None.

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/s/

ANN T FARRELL
12/18/2017

Division of Hematology Products
Medical Officer's Review

NDA #:	208843
Application Type:	505(b)(2)
Drug:	Siklos® (Hydroxyurea)
Therapeutic Class:	Antineoplastic
Proposed Indication:	To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises.
Formulation:	Tablet (100 mg, 1000 mg)
Dosing Regimen:	20 mg/kg administered orally once daily. May increase by 5 mg/kg/day every 8 weeks to a maximum of 35 mg/kg/day
Applicant:	Addmedica SAS
Primary Reviewer:	Rachel Ershler, MD
Clinical Team Leader:	Nicole Gormley, MD
Date Received:	June 30, 2017
PDUFA Goal Date:	December 30, 2017

Executive Summary and Recommended Regulatory Action

Addmedica SAS submitted an original 505(b)(2) application on July 29, 2016 for Siklos® (hydroxyurea) for the following proposed indication: to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older with sickle cell anemia with moderate to severe painful crises. At that time, because of deficiencies identified (b) (4) a Complete Response (CR) letter was issued by the FDA on February 9, 2017. On June 30, 2017, the Applicant provided a resubmission to address the deficiencies identified in the CR letter. There were no clinical deficiencies identified in the initial submission, and the clinical team recommended regular approval of the initial 505(b)(2) application (see Clinical Review dated January 13, 2017). This recommendation was based on the clinical data from Study ESCORT-HU, a multicenter, prospective, non-interventional cohort study, which demonstrated an increase in hemoglobin F values, and a decrease in the overall frequency of painful vaso-occlussive crises in pediatric patients with symptomatic sickle cell disease.

This application was also supported by the Agency's previous finding of safety and efficacy of Droxia® (Hydroxyurea Capsules). Additionally, literature on the use of hydroxyurea for the treatment of sickle cell disease in pediatric patients was provided to support the efficacy and safety in pediatric patients.

The resubmission included a safety update. At the time of the data cutoff for this submission (February 17, 2017), the overall number of subjects (adult and pediatric patients) enrolled on ESCORT-HU who received Siklos® has increased from 992 to 1294. Of these, a total of 627 subjects were ≤18 years of age (increased from 405 in the previous submission). There were no new safety signals identified and the safety profile of Siklos® has remained unchanged.

This Clinical Reviewer recommends regular approval for Siklos® for the indication, "to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises."

Safety Update
A safety update was provided with a data cutoff of February 17, 2017. The size of the pediatric safety database has increased from 405 subjects at the time of previous review to 627 subjects. Of these, 244 (39.0%) had previously received hydroxyurea therapy prior to starting therapy with Siklos®, and 382 (61.0%) were treatment naïve.

Baseline Demographics
Baseline demographic information is provided in the table below.

Table 1. Baseline Demographics and Disease Characteristics of Safety Population

	Global Safety Set N=627 n(%)
Gender	
Male	327 (52.2)
Female	300 (47.8)
Age (years)	
Mean ± SD	9.56 ± 4.52
Range	0.8;18.0
Age Category	
2-10 years	215 (53.9)
10-16 years	149 (37.3)
>16 years	35 (8.8)
Previous HU Treatment	
No	382 (61.0%)
Yes	244 (39.0%)
Missing	1

Source: FDA Clinical Reviewer, Adapted from ESCORT-HU Safety Update

The reason for hydroxyurea initiation is provided in the table below.

Table 2. Reason for Hydroxyurea Initiation

	Global Safety Set N=627 n(%)
Painful Crisis	357 (57.1)
Acute Chest Syndrome	121 (19.4)
Anemia	65 (10.4)
Abnormal TCD	27 (4.3)
Sickle Cell Organopathy	17 (2.7)
Cerebral Vasculopathy	15 (2.4)
Priapism	5 (0.8)

Source: FDA Clinical Reviewer, Adapted from ESCORT-HU Safety Update

Exposure and Treatment Modifications

The exposure and treatment modifications for the pediatric safety population are presented in the table below. Pediatric patients treated with Siklos® received treatment for a median of 20 months. The average dose received was 17.67 ± 4.27 mg/kg/day.

Table 3. Siklos® Exposure and Treatment Modifications

	Global Safety Set N=627 n(%)
Duration of Treatment (months), n	627
Mean ± SD	23.7 ± 19.9
Median	20
Min, Max	0, 92
Dosage (mg/kg/day), n	615
Mean ± SD	17.67 ± 4.27
Median	17.0
Min, Max	2.0, 35.0
Missing (n)	12
Subjects with ≥ 1 Treatment Modification, n(%)	462 (73.7)
Dose Held for >15 Days, n(%)	89 (14.2)
Dose Escalation, n(%)	37 (8.0)

Source: FDA Clinical Reviewer, Adapted from ESCORT-HU Safety Update

The reasons for treatment modification are provided in the table below.

Table 4. Reason for Treatment Modification

	Subjects with Treatment Modification N=462 n(%)
Reason for Treatment Modification, n(%)	
Adjustment for Body Weight	377 (81.6)
Recurrence of VOC	179 (38.7)
Toxicity	25 (5.4)
Bone Marrow Intolerance	18 (3.9)
Patient's Will	12 (2.6)
Other (not specified)	133 (28.8)

Source: FDA Clinical Reviewer, Adapted from ESCORT-HU Safety Update

Major Safety Results

A total of 346 (55.2%) of subjects had 1027 non-sickle cell (non-SCD) related adverse events. Overall, there was one death in the pediatric safety population (Patient #0071), and there were no new deaths in the timeframe since the previous clinical review. An updated summary of the major safety findings is provided in the table below.

Table 5. Major Safety Results

Event	Global Safety Set (N=627) n(%)
Any non-SCD related TEAE	346 (55.3)
Serious non-SCD TEAE	190 (30.3)
Treatment modification due to TEAE	95 (15.2)
Deaths	1 (0.16)
Permanent discontinuation due to TEAE	0 (0.0)

Source: FDA Clinical Reviewer

Non-Sickle Cell Related Adverse Events

A total of 1027 non-SCD related adverse events were reported in 346 (55.2%) pediatric patients in the safety population. The most common adverse events by preferred term are provided in the table below.

Table 6. Non-SCD Treatment-Emergent Adverse Events of Any Grade

Preferred Term	Global Safety Set (N=627) n(%)
Infections and Infestations	215 (34.4)
Bacterial Infection	89 (14.2)
Viral Infections	63 (10.0)
Parvovirus B19	17 (2.7)
Other Infections	117 (18.7)
Blood and Lymphatic System Disorders	111 (17.7)
Neutropenia	58 (9.3)
Thrombocytopenia	35 (5.6)
Anemia	28 (4.5)
Skin and Subcutaneous Tissue Disorders	49 (7.8)
Fever	45 (7.2)
Headache	38 (6.1)
Vitamin D Deficiency	26 (4.1)
Constipation	14 (2.2)

Source: FDA Clinical Reviewer

Summary of Safety Findings

The safety update provided safety data up to a data cutoff of February 17, 2017. The data provided was consistent with the safety data previously reviewed with the initial application. There were no new safety findings and the safety data are consistent with the known safety profile of hydroxyurea in patients with sickle cell disease.

Regulatory Recommendation: Regular Approval

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/s/

RACHEL E ERSHLER
10/16/2017

NICOLE J GORMLEY
10/16/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208843
Priority or Standard	Priority
Submit Date(s)	July 29, 2016
Received Date(s)	July 29, 2016
PDUFA Goal Date	January 29, 2017
Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name(s)	Rachel Ershler (Clinical Reviewer) Yaping Wang (Statistical Reviewer)
Review Completion Date	January 11, 2017
Established Name	Hydroxyurea
(Proposed) Trade Name	Siklos®
Therapeutic Class	Antineoplastic
Applicant	Addmedica SAS
Formulation(s)	Tablet (100 mg, 1000 mg)
Dosing Regimen	20 mg/kg administered orally once daily. May increase by 5 mg/kg/day every 8 weeks to a maximum of 35 mg/kg/day
Indication(s)	To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises
Intended Population(s)	≥ 2 years of age

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Table 1. List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BID	Twice per day
CBC	Complete Blood Count
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma Glutamyl Transferase
HB	Hemoglobin
HbF	Hemoglobin F (Fetal Hemoglobin)
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
HU	Hydroxyurea
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intention-to-treat
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NDA	New Drug Application
NE	Non-Evaluable

NS	Not Significant
PLT	Platelet Count
PRBC	Packed Red Blood Cell
RTC	Reticulocyte Count
SAP	Statistical Analysis Plan
SCA	Sickle Cell Anemia
SCD	Sickle Cell Disease
SD	Standard Deviation
ULN	Upper limit of normal
WBC	White Blood Cell Count

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval for Siklos® (hydroxyurea) for the indication "to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises."

The basis for regular approval of this 505(b)(2) application for Siklos® is the clinical data from Study ESCORT-HU, a multicenter, prospective, non-interventional cohort study, which demonstrated an increase in hemoglobin F values, and a decrease in the overall frequency of painful vaso-occlussive crises in pediatric patients with symptomatic sickle cell disease.

This application is also supported by the Agency's previous finding of safety and efficacy of Droxia® (Hydroxyurea Capsules). Additionally, literature on the use of hydroxyurea for the treatment of sickle cell disease in pediatric patients is provided to support the efficacy and safety in pediatric patients.

1.2 Risk Benefit Assessment

Background
Sickle cell disease (SCD) is the most common inherited red blood cell (RBC) disorder. Approximately 2000 children in the United States (US) are born with SCD each year, with an incidence of 1 in 2474 live births [1,2]. The estimated prevalence of SCD in the US is estimated to be between 70,000 – 140,000 [3]. Sickle cell disease is characterized by heterogeneous disease manifestations, significant morbidity and complications that worsen with age. In the US, the median survival for HbSS and HbSC disease is 58 and 66 years, respectively [4].

Hydroxyurea is the only pharmaceutical agent that is FDA approved for the reduction in the frequency of painful VOCs in patients with SCD. However, neither hydroxyurea nor any other pharmaceutical agent is approved in the US for children with SCD.

Efficacy
The efficacy of Siklos® is based on the results of a large, multicenter, prospective, non-interventional study in subjects age 2 years and older with symptomatic sickle cell disease: ESCORT-HU. The primary efficacy endpoint was the absolute change in HbF level at least 6 months after initiation of Siklos® as compared to HbF level before initiation of Siklos®. HbF is considered a surrogate efficacy variable, as increases in HbF have been associated with improvements in SCD manifestations including, a reduced rate of acute painful episodes, dactylitis, acute chest syndrome and leg ulcers.

A total of 141 subjects were included in the efficacy dataset. For the wider time window (collected between 5 and 14 months; N=47/141, 33%), the median (range) baseline HbF was 5.6% (1.3, 15.0) and the median (range) post-baseline HbF was 12.8% (2.1, 37.2), with a median (range) increase of 5.9% (-2.2, 34.7). Secondary efficacy endpoints included the absolute change in hemoglobin (Hb) after at least 6 months and at 12 months after initiation of Siklos®, as well as the occurrence of SCD events such as painful crisis, acute chest syndrome and hospitalizations.

The clinical benefit of hydroxyurea in pediatric patients is supported by the previous findings of efficacy of Droxia® in adult subjects with SCD (extrapolated to pediatric patients). Efficacy was also supported by the compilation of published studies using hydroxyurea in pediatric patients.

Safety

Assessment of the safety of Siklos® in pediatric patients is based primarily on the safety findings from ESCORT-HU, with support from published studies using hydroxyurea in pediatric patients. In ESCORT-HU, the global safety set consisted of 405 pediatric subjects treated with Siklos®. Among them, 233 subjects were not previously treated with hydroxyurea at the time of Siklos® initiation and were included in the Safety set (SS). An SAE was reported for 27% of subjects in the global safety set. The most frequent non-sickle cell related serious adverse reactions in the global safety set were infections (18.0%), thrombocytopenia (3.7%) and neutropenia (3.0%). The most common non-SCD-related treatment-emergent adverse events of any grade were neutropenia (11.1%), fever (8.1%), thrombocytopenia (5.7%), rash (5.7%) and headache (5.7%). In the ESCORT-HU study, there was one death in a pediatric patient. This event was considered to be not related to Siklos® treatment.

Overall Benefit-Risk Assessment for the Proposed Indication

Approval of Siklos® to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients 2 years of age and older with SCD and moderate to severe painful crises is based on the results from study ESCORT-HU, as well as the previous findings of safety and efficacy of Droxia® in adults with SCD, with support from the published literature of hydroxyurea use in pediatric patients with SCD.

Siklos® use results in an overall increase in hemoglobin F and clinically meaningful decreases in SCD-related events. The safety profile of Siklos® was similar to that already known with hydroxyurea. It is recommended that the label contain a boxed warning for myelosuppression and malignancies. Additional warnings and precautions include embryo-fetal toxicity, cutaneous vasculitic toxicities, risks with concomitant use of antiretroviral drugs, and concomitant use with live virus vaccines. The risk-benefit assessment supports regular approval for the proposed indication.

Table 2. Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions
Analysis of Condition	Sickle Cell Disease (SCD) is the most common inherited red blood cell (RBC) disorder. Approximately 2000 children in the United States are born with SCD each year, with a disease incidence of 1 in 2474 live births [1,2]. SCD has many disease manifestations. Vascular injury from chronic ischemia leads to multi-organ dysfunction and early death.	SCD is a serious and life-threatening condition.
Unmet Medical Need	SCD is a chronic disease characterized by multiple disease manifestations and complications. Hydroxyurea (Droxia®) is the only agent FDA approved for use in patients with SCD. However, it is only approved for use in adults. There are no agents approved in the US for children with SCD.	SCD is a serious and life-threatening disease with significant morbidity. Therapeutic options are needed for children with SCD.
Clinical Benefit	The clinical benefit of Siklos® in pediatric patients was determined by the efficacy results of Study ESCORT-HU, as well as the previous findings of efficacy of Droxia® in adult subjects with SCD (via extrapolation to pediatric patients). Efficacy was also supported by data from two published controlled studies with the same target indication as Siklos® [5,6], three published controlled studies in pediatric patients with SCD [7,8,9], one long-term follow-up study of registries in Belgium and France [10], and 18 additional open-label, non-controlled studies. Hemoglobin F (HbF) is considered a surrogate efficacy variable, as increases in HbF inhibit the deoxygenation-induced polymerization of sickle hemoglobin (HbS) that drives the pathophysiology of SCD. ESCORT-HU was a multicenter, prospective, non-interventional study of Siklos® in subjects ≥ 2 years of age with symptomatic SCD. The initial starting dose was 15 mg/kg/day, which was titrated by 5 mg/kg increments every 8 weeks to a maximum dose of 35 mg/kg/day. • After at least 6 months of treatment with Siklos®, there was an increase from baseline in Hemoglobin F (8.01 ± 8.38%). • The number of clinical events decreased in the 12 months after Siklos® initiation when compared to the 12 months prior to treatment.	Siklos® use resulted in an increase in hemoglobin F, which has been associated with improvements in clinical manifestations in patients with SCD. Siklos® use was shown to demonstrate an improvement in several key sickle cell disease manifestations including painful crises, acute chest syndrome, number of hospitalizations, days of hospitalization, and number of patients requiring blood transfusions.

	• The number of patients with ≥1 painful crisis in the preceding 12 months decreased from 83 (69.2%) at baseline to 51 (42.5%) at 12 months (120 evaluable patients). • The number of patients experiencing at least one episode of acute chest syndrome decreased from 29 (23.6%) at baseline to 7 (5.7%) patients at 12 months (123 evaluable patients). • The number of patients with at least 1 hospitalization related to SCD decreased from 83 (75.5%) at baseline to 46 (41.8%) at 12 months (110 evaluable patients). • Decreases were also seen in the number of patients who received at least 1 transfusion.	
Risks	The safety population for Study ESCORT-HU included 405 pediatric subjects in the Global Safety Set. • The median duration of exposure to Siklos® was 18 months • Serious adverse reactions (including both SCD-related events and non-SCD related events) were reported in 109 (26.9%) of subjects. • The most frequent non-SCD related events were bacterial infections (11.9%), neutropenia (11.1%), and viral infections (7.4%). • One death in a pediatric patient (unrelated to Siklos® treatment)	Younger children appear to have an increased risk of myelosuppression, particularly neutropenia, when compared to older children and adults. All pediatric patients should be monitored regularly for myelosuppression, particularly at the time of dose adjustments for increased body weight.
Risk Management	Prescribers should be aware of the risks of myelosuppression, the potential for secondary malignancies, embryo-fetal toxicity, cutaneous vasculitic toxicities, risks with concomitant use of antiretroviral drugs and live virus vaccines. The proposed labeling includes warnings and precautions including recommended monitoring, and dose modifications. Safe use will require that both patients and healthcare providers are aware of these instructions.	It is recommended that the label contain a boxed warning for myelosuppression and malignancies. Additional warnings and precautions include embryo-fetal toxicity, cutaneous vasculitic toxicities, risks with concomitant use of antiretroviral drugs, and concomitant use with live virus vaccines.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

Sickle Cell Disease (SCD) is the most common inherited red blood cell (RBC) disorder. Worldwide, it is estimated that over 200,000 children affected with SCD are born every year, primarily in sub-Saharan Africa (180,000 births per year) [11]. Approximately 2000 children in the United States (US) are born with SCD each year, with a disease incidence of 1 in 2474 live births [1, 2]. The estimated prevalence of SCD in the US ranges from 70,000-140,000 [3]. In the US, the median survival for HbSS and HbSC disease is 58 and 66 years, respectively [4].

SCD results from a single genetic point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of hemoglobin. This mutation leads to an abnormal form of hemoglobin, known as sickle hemoglobin (HbS). People who inherit two copies of the HbS mutation are homozygous (HbSS) and have the disease phenotype, whereas heterozygous carriers (HbAS) have sickle cell trait and do not exhibit clinical disease. The abnormal HbS results in deformed and fragile RBCs that have a characteristic sickle shape and a reduced lifespan [12]. The sickled RBCs occlude the microvascular circulation, which leads to tissue ischemia, infarctions and chronic hemolytic anemia.

SCD is characterized by heterogeneous disease manifestations and complications that worsen with age including acute vaso-occlussive crises (VOCs), chronic pain, chronic hemolytic anemia, recurrent infections, and neurologic complications. Additionally, vascular injury from chronic ischemia leads to multi-organ dysfunction and early mortality [13]. In infants and children, SCD may cause poor nutritional status and delayed growth and puberty.

VOCs are the most common acute manifestation of SCD and cause significant morbidity [13]. Hydroxyurea is the only pharmaceutical agent that is FDA approved for the reduction in the frequency of painful VOCs in patients with SCD. However, neither hydroxyurea nor any other pharmaceutical agent is approved in the US for children with SCD. Therefore, there is a great need for novel and effective treatments in this patient population.

2.1 Product Information

Established Name: Hydroxyurea

Trade Name: Siklos®

Chemical Class: Urea, new dosage form

Pharmacologic Class: Antimetabolite

Proposed Indication: To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises.

Proposed Dosage and Administration:
- Initial dose: 20 mg/kg/day as a single dose
- Titration: Increase dose by 5 mg/kg/day every 8 weeks or if a vaso-occlusive crisis occurs. Titrate dose until mild myelosuppression occurs (defined as an absolute neutrophil count 2,000/µL – 4,000/µL), up to a maximum dose of 35 mg/kg/day.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 3. Available medications for the reduction in the frequency of VOCs in SCD

Therapy	Target
Hydroxyurea*	Inhibition of DNA synthesis, immune-modulation, increase hemoglobin F in RBCs

*Currently only approved for use in adults
Source: FDA Clinical Reviewer

2.3 Availability of Proposed Active Ingredient in the United States

Hydroxyurea (HU) is a cytotoxic, antimetabolite, and antineoplastic agent that has been used for several decades to treat a variety of medical disorders, and is marketed worldwide including in the US, Canada, and Europe. Two forms of Hydroxyurea are currently available in the US. Hydrea® (hydroxyurea capsules) was approved in 1967 and has shown activity in a variety of cancers including melanoma and carcinoma of the ovary. It is currently indicated for the treatment of resistant CML as well as locally advanced squamous cell carcinomas of the head and neck, excluding the lip. Droxia® (hydroxyurea capsules) was approved in the US in 1998 and is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with SCD with recurrent moderate to severe painful crises.

Hydroxyurea in Pediatric Patients with SCD
The use of hydroxyurea in pediatric patients is currently off-label. Pediatric patients are often administered compounded liquid formulations of hydroxyurea. To date, several randomized controlled trials have been conducted in the US to address the safety and efficacy of hydroxyurea in pediatric patients with SCD, as summarized in section 7.1.1.

2.4 Important Safety Issues With Consideration to Related Drugs

The Droxia® label contains warnings for myelosuppression and malignancies.

Myelosuppression
Hydroxyurea may cause severe myelosuppression and should not be given if bone marrow function is markedly depressed. Blood counts should be monitored at baseline and throughout treatment. Hydroxyurea should be dose reduced or discontinued as necessary.

Malignancies
Hydroxyurea is carcinogenic. Advise patients on the need for sun protection. Patients should be monitored for the occurrence of malignancies.

Additional warnings and precautions include:

- Embryo-fetal toxicity: (b) (4) cause fetal harm. (b) (4) advised of potential risk to a fetus and use effective contraception.
- (b) (4) vasculitic toxicities
- Risks with concomitant use of antiretroviral drugs: Pancreatitis, hepatotoxicity and neuropathy have occurred. (b) (4)

The most common adverse reactions (≥30%) with Droxia® use are hematological, gastrointestinal symptoms and anorexia.

See section 7.3.4 for additional details.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Siklos® was approved in the EU in June 2007 and first marketed in Europe in March 2008. The foreign marketing history is provided in Table 4 below.

A summary of the regulatory history of Siklos® is outlined in the table below.

Table 4. Siklos® Regulatory History

Date	Event Type	Purpose
July 23, 2013	Orphan Designation Granted (Designation # 13-4004)	
December 11, 2014	Pre-NDA meeting	To discuss the legal basis and content of the NDA package
October 22, 2015	Type C Meeting	To discuss the clinical content of the NDA
June 14, 2016	Type C meeting	To discuss the clinical content of the NDA

Source: FDA Clinical Reviewer

The EMA required a Risk Management Plan to collect information regarding the long-term safety of Siklos® in patients with sickle cell disease. ESCORT-HU was planned and conducted to meet the requirements of the Risk Management Plan (RMP), as requested by the EMA. In the pre-NDA meetings held with the FDA in December 2014 and October 2015, it was agreed that the Applicant would compile clinical efficacy and safety data from ESCORT-HU in pediatric patients to support a 505(b)(2) marketing application in the US.

2.6 Other Relevant Background Information

To support this 505(b)(2) application, in addition to data from the pivotal ESCORT-HU study, the Applicant is relying on the previous findings of safety and efficacy of the reference drug, Droxia®, which is currently approved for use to reduce the frequency of painful crises and to reduce the need for blood transfusions in adults with sickle cell anemia with recurrent moderate to severe painful crises.

Assessment of the efficacy of Siklos® in pediatric patients is based on the results of Study ESCORT-HU with support from the previous findings of efficacy of Droxia® in adult subjects with SCD (via extrapolation to pediatric patients), and with support from the literature.

Assessment of the safety of Siklos® in pediatric patients is based primarily on the safety findings from Study ESCORT-HU, with support from published studies using hydroxyurea in pediatric patients (see below).

Supportive Literature Studies

To support this application, the Applicant is relying on data from 28 available published studies of hydroxyurea in pediatric patients with sickle cell disease. Of these, two are controlled studies in the same target indication [5,6], three are published controlled studies in pediatric patients [7,8,9], and 23 are comparative, non-controlled studies.

Below is a summary of the clinical trial design and topline results for the published controlled studies. See Sections 5.1, 6.1.10 and 7.2.6 for additional information.

Published Controlled Studies Used to Support this Application

1. Ferster, Vermylen et al. 1996 [5]

This was a randomized cross-over study conducted in Belgium of 25 children and young adults (age range: 2 to 22 years) with homozygous sickle cell anemia and severe clinical manifestations (defined as >3 vaso-occlusive crises in the year before study entry and/or with previous history of stroke, acute chest, recurrent crises without a free interval, or splenic sequestration). The primary outcome measure of the study was the number and duration of hospitalizations.

Patients were randomly assigned to receive either hydroxyurea first for 6 months, followed by placebo for 6 months, or placebo first, followed by hydroxyurea for 6 months. Hydroxyurea was administered at an initial dose of 20 mg/kg/day. The dose was increased to 25 mg/kg per day if change in hemoglobin F was <2% after 2 months. Dose was reduced by 50% for bone marrow toxicity.

Overall, the number and duration of hospitalizations were significantly reduced for patients on hydroxyurea compared to placebo. Results of this study are presented in Tables 5 and 6 below.

The authors of this study concluded that treatment with hydroxyurea in children and young adults is well-tolerated and improves the clinical course of sickle cell anemia.

Table 5. Hospitalizations and Days in Hospital by Treatment

	HU (N=22)	Placebo (N=22)
No of Hospitalizations		
0	16	3
1	2	13
2	3	2
3	0	3
4	1	0
5	0	1
No. of Days in Hospital		
0	16	3
1-10	2	13
> 10	4	6
Range	0-19	0-104

Source: Ferster, Vermylen et al. 1996, Table 4

Table 6. Mean (± SD) Hematological Values Before and After 6 Months of Treatment with Hydroxyurea

Variable	Before HU	After HU	p value
Hb (g/dL)	8.1±0.75	8.5±0.83	NS
MCV (fL)	85.2±9.74	95.5±11.57	<0.001
MCHC (%)	33.0±2.08	32.3±1.12	NS
PLT ($x10^9$/L)	443.2±189.1	386.7±144.6	NS
WBC ($x10^9$/L)	12.47±4.58	8.90±2.51	<0.001
HbF (%)	4.65±4.81	15.34±11.3	<0.001
RTC (‰)	148.6±53.8	102.7±48.5	<0.001

Source: Ferster, Vermylen et al.1996, Table 2

2. Jain, Sarathi et al. 2012 [6]

This was a prospective, double-blind, randomized, placebo-controlled study conducted in 60 Indian patients age 5 to 18 with severe sickle cell anemia (defined as frequent vaso-occlusive crises requiring hospitalization (>3 per year)). Patients were randomized to receive either hydroxyurea (n=30) at a fixed dose of 10 mg/kg/day or placebo (n=30) for 18 months. The primary outcome was the decrease in the frequency of vaso-occlusive crises per patient per year. Secondary outcomes included the decrease in frequency of blood transfusions and hospitalizations, and the increase in hemoglobin F levels.

After 18 months, patients in the hydroxyurea arm had significantly higher hemoglobin and HbF levels, compared to those who received placebo. Results of this study are summarized in Table 7 below.

Table 7. Change (Mean SD) in Hemoglobin and HbF Parameters

	Hydroxyurea group N=30		Placebo group N=30			
Parameters	Baseline	After 18 months	Baseline	After 18 months	p Value[a]	p Value[b]
Hb (g/dL)	8.10 ± 0.68	9.29 ± 0.55	8.21 ± 0.68	7.90 ± 0.5	0.27	<0.001
Hb F (%)	19.80 ± 6.9	24.00 ± 5.90	19.21 ± 6.37	18.92 ± 5.7	0.11	<0.001

Source: Jain, Sarathi et al. 2012, Table 1

3. BABY HUG [7]

BABY HUG was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of hydroxyurea in infants in the US between 2003 and 2009. Eligible participants were aged 9-18 months at the time of randomization and had hemoglobin SS (HbSS) or hemoglobin Sβ0thalassemia. Subjects were randomized to receive liquid hydroxyurea 20 mg/kg/day or placebo for two years. Primary study endpoints were splenic function (qualitative uptake on 99Tc spleen scan) and renal function (glomerular filtration rate). Additional assessments included blood counts, HbF concentration, chemistry profiles, spleen function, biomarkers, transcranial Doppler (TCD) ultrasonography results, and

mutagenicity. In total, 96 patients received hydroxyurea and 97 received placebo. Of these, 83 the hydroxyurea group and 84 in the placebo group completed the study. There were no significant differences between the groups for either of the primary endpoints (19/70 patients with decreased spleen function in the hydroxyurea group vs 28/74 in the placebo group, p=0.21; difference in the mean increase in GFR in the hydroxyurea group vs the placebo group of 2 mL/min per 1.73 m2, p=0.84). However, hydroxyurea significantly decreased the number of painful events (177 events in 62 patients vs 375 events in 75 patients, p=0.002) and dactylitis (24 events in 14 patients vs 123 events in 42 patients, p<0.0001), with some evidence of decreased episodes of acute chest syndrome, hospitalization rates and transfusions. Hydroxyurea increased HbF and decreased WBC. The most common toxicity was mild-moderate neutropenia.

On the basis of the safety and efficacy data from this trial, the authors recommended hydroxyurea to be considered for all very young children with SCA.

4. SWiTCH [8]

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) was a multicenter phase 3 randomized trial comparing standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/phlebotomy) for children with SCD, stroke and iron overload. SWiTCH was a non-inferiority trial with a composite primary endpoint of secondary stroke recurrence rate and quantitative liver iron content (LIC). Secondary endpoints included non-stroke neurologic events, non-neurologic sickle cell clinical events, quality of life and measures of organ function.

Subjects on the standard treatment received monthly transfusions plus daily deferasirox iron chelation. Subjects on the alternative treatment arm received hydroxyurea plus overlap transfusions during dose escalation to the MTD, followed by monthly phlebotomy. Sixty out of 67 (90%) subjects on the alternative treatment arm reached the MTD. There were no strokes on the transfusion/chelation arm and 7 (10%) on the hydroxyurea/phlebotomy arm, still within the non-inferiority stroke margin. The National Heart, Lung, and Blood Institute closed SWiTCH after interim analysis revealed equivalent liver iron content, indicating futility for the composite primary endpoint. The investigators concluded that transfusions and chelation remain a better way to manage children with SCD, stroke and iron overload.

5. TWiTCH [9]

TCD with Transfusions Changing to Hydroxyurea (TWiTCH) was an NHLBI-funded Phase III multicenter, randomized clinical trial comparing 24 months of standard treatment (transfusions) to alternative treatment (hydroxyurea) in 121 children age 4-16 years with SCD and abnormal TCD velocities (≥200 cm/s) but no severe vasculopathy. Subjects assigned to standard treatment (N=61) continued to receive monthly transfusions to maintain 30% HbS or lower, while those assigned to the alternative

treatment (N=60) started oral hydroxyurea at 20 mg/kg/day, which was escalated to each participant's maximum tolerated dose. This study used a non-inferiority trial design with a primary endpoint of TCD velocity at 24-months, controlling for baseline (enrollment) values. The non-inferiority margin was 15 cm/sec. At the first scheduled interim analysis, non-inferiority was shown and the Sponsor terminated the study. Final model-based TCD velocities were 143 cm/s (95% CI 140-146) in children who received standard transfusions and 138 cm/s (95% CI 135-142) in those who received hydroxyurea, with a difference of 4.54 (0.10-8.98). Non-inferiority (p=8.82x10-16) and post-hoc superiority (p=0.023) were met. Based on these results, the investigators concluded that for children with SCD and abnormal TCD velocities who have received at least 1 year of transfusions, and have no MRA-defined severe vasculopathy, hydroxyurea treatment may substitute for chronic transfusions to maintain TCD velocities and help prevent primary stroke.

Current Use of Hydroxyurea in Pediatric Patients with SCD

In 2002, the National Heart, Lung, and Blood Institute (NHLBI) issued recommendations supporting the use of hydroxyurea for the treatment of children with SCD. In current clinical practice, NHLBI treatment guidelines recommend the use of hydroxyurea for children age 9 months and older with sickle cell anemia to reduce the frequency of sickle cell-related pain and the incidence of acute chest syndrome [14]. However, the use of Droxia® in pediatric patients is currently off-label.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was provided in accordance with the International Conference on Harmonization Electronic Common Technical Document (eCTD).

Overall, the datasets provided were poor quality and limited the ability of a thorough analysis. There was an extensive amount of missing data in the datasets provided and some of the coding was not in English. The initial datasets lacked treatment initiation dates and accurate adverse event coding. Laboratory datasets were missing a large amount of data as well as the normal ranges. Multiple requests for additional information were sent to the Applicant during the review period, including requests for exposure data, treatment start dates, and conversion of data to English. Individual dataset deficiencies will be discussed in each specific review subsection.

3.2 Compliance with Good Clinical Practices

ESCORT-HU was a prospective study conducted under 2 IECs (Appendix 1 of CSR).

3.3 Financial Disclosures

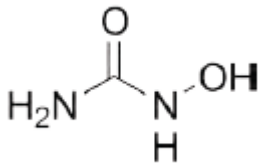
The applicant submitted financial disclosure information for investigators. There were no principal investigators or sub-investigators from Study ESCORT-HU who reported financial interest or arrangements as described in 21 CFR 54.4(a)(3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Siklos® is a highly potent anti-metabolite with a simple chemical structure, as shown in the figure below.

Figure 1. Chemical Structure of Hydroxyurea



Siklos® film coated tablet is presented in two strengths, 100 mg or 1000 mg of hydroxyurea. The 1000 mg tablet has score lines so that it can be divided into four equal parts. The formulation of hydroxyurea, allows dosing in 100 mg and 250 mg intervals.

Siklos® 100 mg film-coated tablet is a white to off-white round biconvex tablet engraved “100” on one side and with a diameter of approximately 6 mm.

Siklos® 1000 mg film-coated tablet is a white to off-white capsule-shaped tablet engraved “T⊥T⊥” on one side, with 3 breaking notches on both sides and with a length of approximately 22 mm.

Refer to the CMC Review for further details.

4.2 Clinical Microbiology

Refer to the CMC Review.

4.3 Preclinical Pharmacology/Toxicology

The pharmacokinetic profile of hydroxyurea has been characterized in mice, rats, dogs and humans. Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. Hydroxyurea is 75-80% unbound to serum proteins and distributes rapidly and widely in the body, with an estimated volume of distribution approximating total body water. Hydroxyurea is rapidly excreted into the urine of mice, rats and humans, with smaller contributions by respiratory and fecal routes. Hydroxyurea does not appear to influence they cytochrome P450 pathway.

In multiple-dose toxicity studies in rats (10 days) and dogs (2 weeks and 1 month), hydroxyurea was shown to cause hematopoietic, lymphoid, cardiovascular, and gastrointestinal toxicity with steep dose response curves. The NOAEL was 50 mg/kg/day in both rats and dogs.

Refer to the Pharmacology-Toxicology Review for further details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

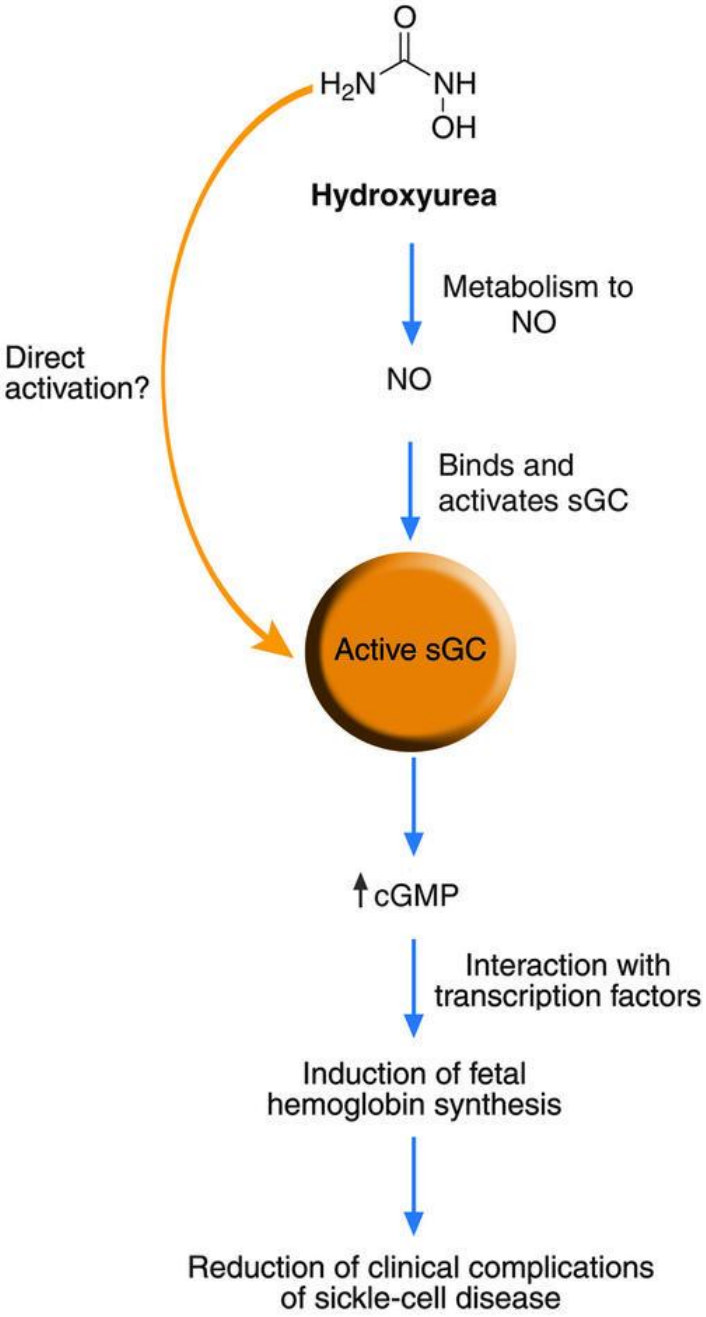
The mechanism of action of hydroxyurea in sickle cell disease is multifactorial, and includes the following:

- Inhibition of the enzyme ribonucleotide reductase.
- Increased hemoglobin F (HbF)
- Decrease in the number of circulating leukocytes and reticulocytes, as well as alteration of the expression of adhesion molecules, all of which contribute to vaso-occlusion.
- Increased red blood cell (RBC) volume, which improves cellular deformability, increasing blood flow and decreasing vaso-occlusion.
- Release of nitric oxide (NO), which may contribute to local vasodilation

The mechanism of the clinical benefit of hydroxyurea in patients with SCD is not fully elucidated, and is likely multi-factorial. However, the principle and most well understood mechanism is the reversible inhibition of ribonucleotide reductase, which ultimately results in increased HbF. In patients with SCD, HbF inhibits intracellular HbS polymerization and prevents the sickling process within erythrocytes [15]. A high HbF is associated with improvements in SCD manifestations including a reduced rate of acute painful episodes, dactylitis, acute chest syndrome and leg ulcers [16]. Other potential benefits of hydroxyurea in this patient population include decreased expression of surface molecules that adhere to the endothelium, decreased chronic inflammation (decrease WBC and platelet counts), and increased levels of nitric oxide and cyclic nucleotides that may facilitate vascular dilation [16].

The increase in HbF leads to decreased red blood cell (RBC) damage and hemolysis, which is beneficial in patients with SCD. The mechanism of HbF induction by hydroxyurea is demonstrated in the Figure 2.

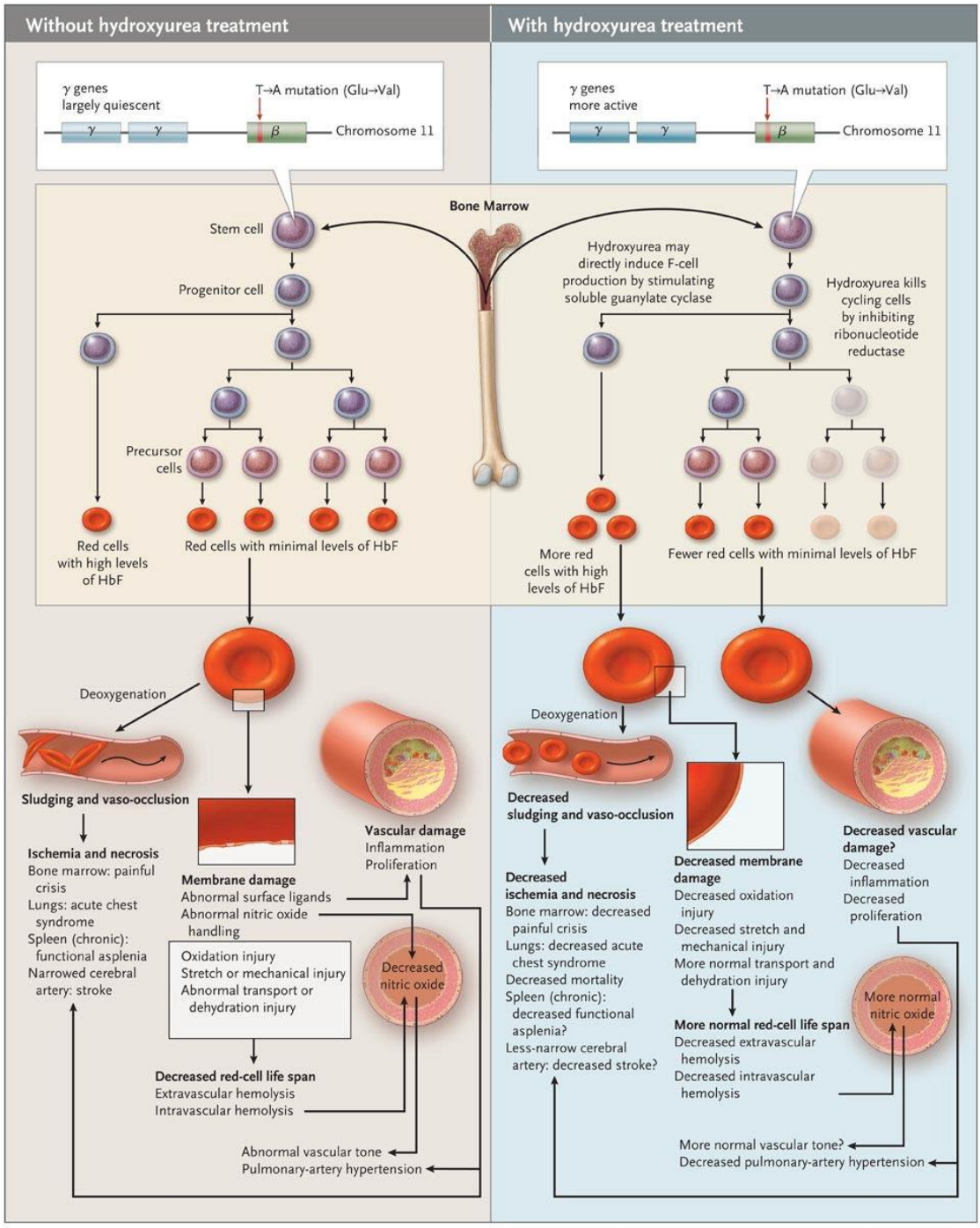
Figure 2. Mechanism of Fetal Hemoglobin Induction by Hydroxyurea



Source: King. J. Clin Invest. 2003. Figure 1 [15]

Figure 3 below depicts the pathophysiological characteristics of Sickle Cell Anemia and the effects of hydroxyurea.

Figure 3. Effects of Hydroxyurea on the Pathological Characteristics of Sickle Cell Anemia



Source: Platt. N Engl J Med. 2008. Figure 1 [16]

4.4.2 Pharmacodynamics

Refer to section 4.4.3 and the Clinical Pharmacology Review for further details.

4.4.3 Pharmacokinetics

The Siklos® clinical pharmacology development program included one Phase 1 PK study of Siklos® 1000 mg tablets in pediatric, adolescent and young adult patients with SCD (Study OTL-001-01). This study provides the PK data for Siklos® at doses of 14 to 36 mg/kg/day for 14 days in pediatric patients.

Because the absorption of hydroxyurea is rapid and appears to be unaffected by the dose form used for delivery (tablet, capsule or liquid), the published data from studies using any oral formation of hydroxyurea in the target population is included in this application as further evidence of the PK profile of hydroxyurea.

Absorption
In study OTL-001-01, following repeat daily tablet administration over 14 days (mean daily dose of approximately 20 mg/kg, range 14 to 36.5 mg/kg) in 11 pediatric patients, Siklos® showed overall excellent oral bioavailability with rapid, but variable absorption (mean t_{max} 0.75 hours, mean C_{max} 29.61 mg/L). Median $AUC_{0-\alpha}$ was 116 mg/L/hr. There is limited data on dose linearity of hydroxyurea in pediatric subjects. However, in adult patients, the plasma hydroxyurea level at 2 hours post administration of drug was correlated linearly with drug dose ($r=0.48$, $p<0.0001$) within the dose ranges studied (10 to 35 mg/kg).

Distribution
Hydroxyurea is not highly bound to plasma proteins and distributes rapidly throughout the human body, including the CSF, and concentrates in leukocytes and erythrocytes. The volume of distribution (V_d) of hydroxyurea approximates total body water. The mean volume of distribution at steady state adjusted for bioavailability is 0.57 L/kg in pediatric patients with SCD.

Metabolism
The biotransformation pathways of hydroxyurea, as well as the metabolites, are not fully characterized. Hydroxyurea appears to be degraded to urea in the liver and kidney. It is not metabolized by cytochrome p450, and is not a P-gp substrate.

Excretion
In pediatric patients with SCD, hydroxyurea is rapidly eliminated with a half-life of 7.49 hours. The mean rate of clearance is 0.20 L/hr/kg.

In pediatric patients, exposure to Siklos® at an initial daily dose of 20 mg/kg followed by daily dosing and titration every 8 weeks up to maximum tolerated dose (MTD) is

considered to provide sufficient serum concentrations of hydroxyurea to elicit a biological and clinical response to treatment.

Effect of Age on Siklos® Pharmacokinetics

The pharmacology, safety and efficacy of hydroxyurea in adults with SCA is well established. In study OTL-001-01, the PK of hydroxyurea was evaluated after administration of Siklos® to both pediatric and adult patients. In pediatric patients compared to adult patients with sickle cell disease who were treated with Siklos® 1000 mg tablets, C_{max} and AUC were similar, whereas $t_{1/2}$ and C_{trough} were increased and t_{max} and urinary elimination were decreased. Age differences in PK are also reported in several published studies. The reasons for the PK differences between pediatric and adult patients are unknown. However, because of the overall similar systemic exposure to hydroxyurea (AUC and C_{max}), and because the dose is adjusted by body weight, a similar dosing regimen to that already used in adult patients can be adopted in pediatric patients aged 2 years and over to reach the maximum tolerated dose (MTD).

Siklos® Bioequivalence

The Applicant submitted a bioequivalence study to support this application. However, this was deemed inadequate because of the lack of bioanalytical raw data and the lack of a bioanalytical report. However, upon review, the OCP review team determined that hydroxyurea (b) (4)

(b) (4)

Refer to the Clinical Pharmacology and OBP Reviews for further details.

5 Sources of Clinical Data

The safety and efficacy of Siklos® in subjects 2 years of age and older with sickle cell disease is based on two clinical studies of Siklos® conducted in pediatric patients, including a Phase 1, prospective, open-label PK study of Siklos® 1000 mg tablets (Study OTL-001-01), and the pivotal ESCORT-HU study. ESCORT-HU was planned in the context of the Risk Management Plan (RMP), as requested by the EMA to collect information regarding the long-term safety of Siklos® in patients with sickle cell disease. An overview of the clinical trials reviewed is provided in Table 8.

The safety and efficacy of hydroxyurea in pediatric patients with sickle cell disease is also supported by five published controlled studies in pediatric patients (Table 9), one open, long-term follow-up study of registries of pediatric patients with sickle cell disease in Belgium and France, and 23 additional published non controlled studies in pediatric patients with sickle cell disease.

5.1 Tables of Studies/Clinical Trials

Table 8. Clinical Trials Reviewed

Trial Identifier (Identifier of Study Report) Type of Study	Trial Design	Trial Objective(s)	Number of Centers	Patient Population	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Status
OTL-001-01 BE, PK, Safety	Prospective, multicenter, open, Phase 1 study with 2 arms: Group 1: PK of Siklos® in pediatric pts (age <18 yrs) Group 2: PK and BE of Siklos® in adult pts, randomized, cross-over	PK and/or BE in SCD patients under pseudo steady-state conditions. Safety	3 sites in France	SCD (HbSS or HbSβ^0-thal)	Group 1: Siklos® 1000 mg tablets, oral dose 15-25 mg/kg/day before breakfast (fasted state) over 14 days Group 2: Siklos® 1000mg tablets and Hydrea® 500 mg capsules, oral dose 15-25 mg/kg/day before breakfast (fasted state), each over 8 days (14-28 day washout)	Group 1 Age <18 years: 12 (11 evaluable) Group 2 18 adults (15 evaluable)	Complete

ESCORT-HU European Sickle Cell Disease Cohort Efficacy, Safety	Prospective, non-interventional	1. Comparison of HbF levels before and at least 6 months after initiation of Siklos®. 2. Comparison of Hb levels before and at least 6 and 12 months after initiation of Siklos® 3. Comparison of clinical events before and after 12 months of Siklos® 4. Evaluation of observance and safety	49 Centers in 4 countries (France, Germany, UK, Greece)	Symptom-atic SCD	Siklos® 15 mg/kg/day then adjusted depending on the clinical or hematological response to treatment.	Age <18 years: 445	Ongoing

Source: FDA Clinical Reviewer

Table 9. Supportive Published Controlled Studies

Trial Identifier (Identifier of Study Report) Type of Study	Trial Design	Trial Objective(s)	Number of Centers	Patient Population	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Status
Ferster, Vermylen et al. 1996[5]	Randomized, single-blind, cross-over study. Pts randomized to either HU first for 6 mo then placebo for 6 mo, or placebo for 6 mo then HU for 6 mo.	1. Number of hosp. 2. Number of days in hosp. 3. Number of days of pain	1 (Belgium)	Subjects age 2 to 22 years with severe SCD (>3 VOC in the year prior to study entry)	Hydroxyurea 20 mg/kg/day increased to 25 mg/kg/day if change in HbF was insufficient at 2 months.	25	Complete
Jain, Sarathi et al. 2012[6]	Prospective, double-blind, randomized, placebo-controlled study	1. Decrease in frequency of VOC per patient per year	1 (India)	Subjects with severe SCD (>3 VOC per year and/or >3 blood transfusions per year.	Patients randomized to receive either hydroxyurea 10 mg/kg/day (fixed) or	60	Complete

		2. Decrease in frequency of blood transfusions and hosp. 3. Increase HbF		Age: 5 – 18 years	placebo for 18 months.		
BABY HUG Study[7]	Randomized, rouble-blind, placebo-controlled study	1. Assess the effect of hydroxyurea on organ dysfunction and clinical complications in patients with SCD. 2. Evaluate laboratory findings and toxic effects of hydroxyurea in infants aged 9-18 months	13 in the U.S.	Infants aged 9 -18 months with HbSS or HbSβ^0 thalassemia	Subjects randomized to either hydroxyurea 20 mg/kg/day or placebo for 2 years	193 enrolled (96 hydroxyure a, 97 placebo)	Complete
SWiTCH Study[8]	Multicenter, non-inferiority study	Comparison of hydroxyurea/ phlebotomy to standard treatment (transfusions/ chelation) for reduction of secondary stroke and improvement in iron overload	26 centers	Pediatric patients with Sickle cell anemia, previous stroke, and ≥ 18 months of transfusions with documented iron overload	Subjects randomized to hydroxyurea arm received 20 mg/kg/day with stepwise escalation to MTD	133 enrolled (66 on standard/ control treatment and 67 on hydroxyure a	Complete
TWiTCH Study[9]	Multicenter, open-label, non-inferiority trial	1. Maximum TCD velocity on the index side 2. TCD velocity on the non-index side 3. New stroke or non-stroke neurological events 4. New MRI/MRA lesions 5. Hepatic iron overload 6. Sickle-related events 7. Neuro-psych status 8. Quality of	26 centers in the U.S. and Canada	Pediatric patients aged 4 0 16 years with abnormal TCD flow velocities, but no severe vasculopathy	Subjects randomized to hydroxyurea received 20 mg/kg/day with escalation to MTD	159 enrolled, 121 passed screening (61 on standard group, 60 on alternative group)	Complete

		Life 9. Growth 10. Treatment-related complications					

Source: FDA Clinical Reviewer

5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety data of Study ESCORT-HU, with support from the relevant published literature and from the previous findings of safety and efficacy of the reference listed drug, Droxia®, with extrapolation of the findings in adults to pediatric patients. The electronic submission, with the CSRs were reviewed and analyzed. The key review materials and activities are listed below:

- The electronic submission of the NDA
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to the review team's information requests
- Sponsor presentations to the FDA
- Major efficacy and safety analyses were reproduced or audited

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study OTL-001-01

Study Title: A Phase 1 Pharmacokinetics Study of Hydroxyurea 1,000mg Coated Breakable Tablets and Hydroxyurea 500mg Capsules in Pediatric, Adolescent and Adult Patients Treated for Sickle Cell Syndrome.

Study Design and Study Treatment: This was an open-label, multicenter, phase I study in adult and pediatric patients with SCD (either HbS or HbSβ^0-thalassemia) conducted under pseudo-steady-state conditions. Patients were divided into two groups:

- Group 1: Pediatric/adolescent patients (n=12) who received Siklos® 1000 mg tablets (breakable in 4 parts of 250 mg each) at a target dose of 20 mg/kg/day for 14 days.

- Group 2: Adult patients (n=18) who, using a crossover design, were randomly allocated to receive either Siklos® 1000 mg tablets or Hydrea® 500 mg capsules at a target dose of 20 mg/kg/day for 7 days. Each crossover period was separated by a pseudo wash-out period of 14-28 days, during which patients received Hydrea® capsules.

All subjects were previously treated with hydroxyurea for at least three months and were on a stable dose for at least one month. Study drug was taken as a single oral dose with

half a glass of water before breakfast on each day of the study. Evaluations for PK were performed prior to and over 24 hours following the last dose in each dosing period. PK data were analyzed by a non-compartmental method.

Primary Objective: To provide accurate, detailed and scientifically sound data on the absorption, distribution, metabolism and excretion (ADME) of hydroxyurea tablets (Siklos®) and hydroxyurea capsules in patients with SCD under pseudo-steady-state conditions.

Secondary Objectives:
- Determine the bioequivalence (BE) between the two hydroxyurea forms
- Assess safety and tolerability

Inclusion Criteria (Summarized):
- Males and females with confirmed diagnosis of homozygous SCD or HbSβ^o-thalassemia
- Currently receiving treatment with hydroxyurea capsules (Hydrea®) for at least three months prior to study inclusion with a stable dose for at least one month prior to study inclusion.
- Current daily dose as close to 20 mg/kg as possible (range 15-25 mg/kg)
- Body weight between 12.5-70 kg (study group 1) and 40-100kg (study group 2)
- Written informed consent obtained from subjects older than 18 years.

Additional Inclusion Criteria for Group 1:
- Age 3-18 years
- Use of a reliable method of contraception and a negative urine pregnancy test for female sexually active adolescents of childbearing potential
- Written informed consent from legal representative and the subject (if the subject is intellectually able to understand the implications of his/her participation)

Exclusion Criteria (Summarized):
- Known hypersensitivity to hydroxyurea or other ingredients of the study drug
- WBC <2.5 x 10^9/L
- Platelet Count < 100 x 10^9/L
- Creatinine >120 µmol/L
- ALT >2x ULN
- Infection during the month prior to study
- Blood transfusion during the month prior to study
- Any severe acute or chronic disorder which might impact the PK of hydroxyurea or impair the subject's ability to comply with the study protocol
- Exposure to cytotoxic compounds other than hydroxyurea during the 6 months prior to inclusion in the study

- Participation in another clinical trial in the 3 months preceding inclusion into the study
- Inability to swallow the study drug
- Poor compliance in a former clinical trial

Collection of Adverse Events:
All adverse events were collected and reported, regardless of suspected causal relationship to hydroxyurea.

Dose Modifications for Toxicity: Not included in the protocol.

Study OTL-001-01 Status:
Twelve pediatric patients (mean age 10.25 years, range 4-19 years, body weight 12.5-70 kg) were enrolled. The mean Siklos® dose was 21.3 mg/kg (range 14.0 to 36.5). Eleven subjects completed the study. One subject was withdrawn due to hospitalization for pulmonary infection.

Refer to the Clinical Pharmacology review for additional details.

5.3.2 Study ESCORT-HU

Study Title: ESCORT-HU: European Sickle Cell Disease Cohort - Hydroxyurea

Study Design: ESCORT-HU was conducted as part of the Risk Management Plan required by EMEA. This study is a multi-center, prospective, non-interventional cohort study in male and female patients aged 2 years and older with symptomatic sickle cell disease treated with Siklos® and followed for up to 10 years. Patients were evaluated at inclusion, then every 1 to 4 months according to normal monitoring of the disease. A minimum of yearly follow-up was required.

Following discussion with the Agency during the pre-NDA meeting held on December 11, 2014, it was agreed that the sponsor would compile data on the efficacy and safety of Siklos® in the pediatric population.

Trial Population: Eligible subjects were those age 2 years and older with symptomatic sickle cell disease. Total estimated enrollment is approximately 2000 subjects. At the time of data cutoff, 992 patients were enrolled. Of these, 405 subjects were <18 years of age and were included in the pediatric safety set.

Objectives:
1. To collect information about the long-term safety of Siklos® when used in current practice for the prevention of symptomatic complications in patients with Sickle Cell Disease, assessed based on the frequency of:
    - Myelosuppression (requiring permanent or temporary discontinuation of therapy)

- Malignancies
- Skin ulceration
- Amenorrhea and fertility impairment

2. Secondary safety parameters:
   - Effects of Siklos® on growth and development
   - Outcome of pregnancies: rates of miscarriage, stillbirths, APGAR score at birth, congenital malformations
   - Frequency of serious adverse events
   - Any occurrence of unforeseen safety patterns

3. Overall mortality and survival

4. Occurrence of sickle cell disease events, including:
   - Painful crises
   - Infections
   - Acute chest syndrome
   - Stroke
   - Acute splenic sequestration
   - Hospitalizations due to sickle cell disease events
   - Frequency of blood transfusions

Inclusion Criteria (Summarized):
1. Male or female ambulatory subjects aged 2 years or more (children, adolescents, or adults).

2. Symptomatic sickle cell syndrome.

3. Justifying treatment with Siklos® according to the product indications.

4. Informed of the study by the initiating physician and consenting to participate.

Exclusion Criteria (Summarized): N/A

Study Treatment:
Siklos® 100 mg or 1000 mg tablets were prescribed based on the subject's body weight. The starting dose was 15 mg/kg/day. This dose was adjusted by 5 mg/kg/day increments according to clinical and hematological response. The usual dose was between 15 and 30 mg/kg/day. The maximum dose was 35 mg/kg/day.

Duration of therapy: If the subject continued to respond to therapy either clinically or hematologically (e.g. increase in hemoglobin F, MCV, etc.), they could continue on treatment indefinitely. Patients were to be followed for up to 10 years.

Schedule of Events: N/A

Collection of Adverse Events:
All adverse events were collected and reported, regardless of suspected causal relationship to Siklos®.

Dose Modifications for Toxicity: Not included in the protocol. Siklos® was administered in accordance with the directions in the EU Product Information, which includes dose modification recommendations for toxicity.

Statistics:
All statistical analyses were performed at the 5% significance level. Parameters were summarized using mean, median, standard deviation and range for continuous data and counts or percentages for categorical data. Descriptive statistics were used to report the prevalence of primary and secondary parameters and to describe the global population and subpopulations. Appropriate multivariate analyses were used to describe determinants of the observed events.

Protocol Amendments
One amendment was submitted that contained revisions for study ESCORT-HU.

- Amendment #1 (June 18, 2008): The protocol was amended to include the addition of the assessment of fertility impairment in the objectives.

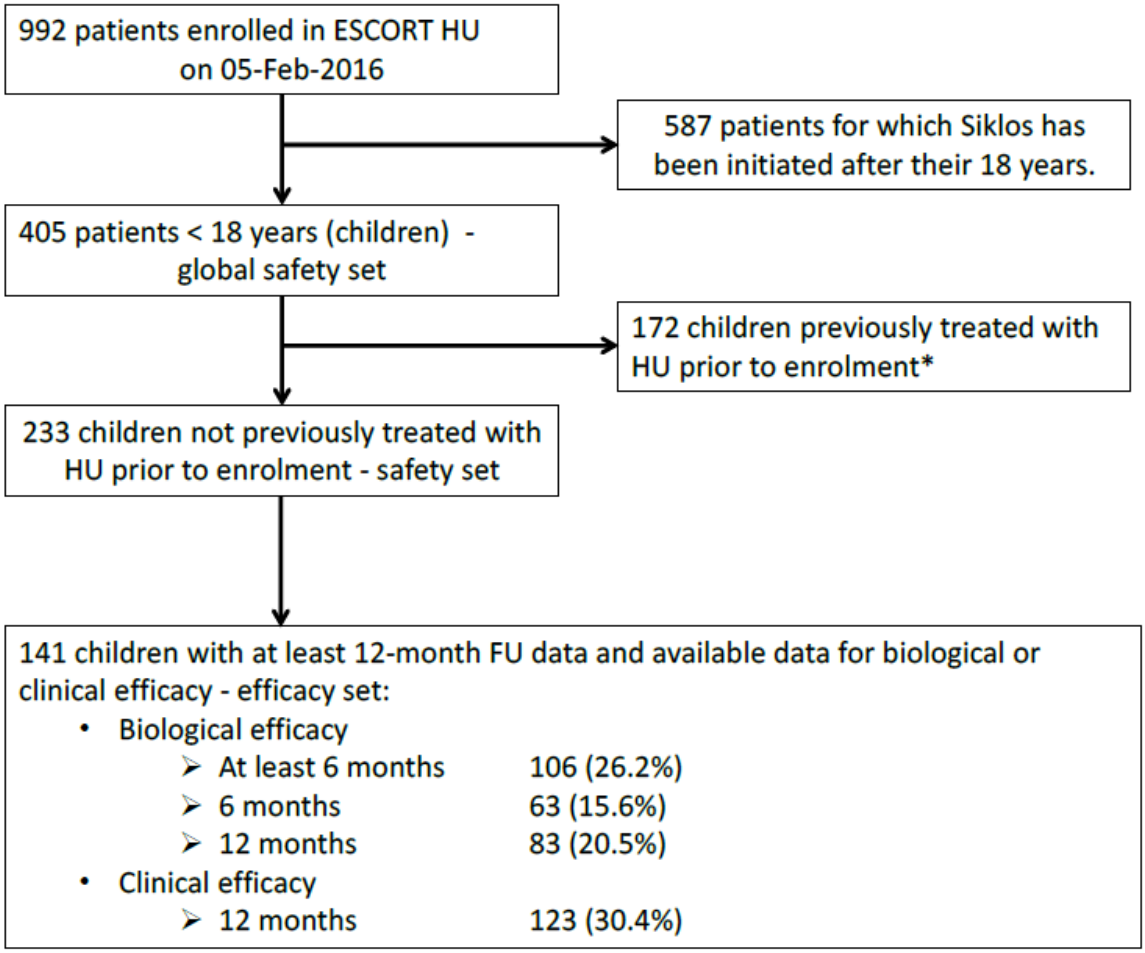
ESCORT-HU Status:
At the time of data cut-off (February 5, 2016), a total of 992 subjects were enrolled. Of these, 405 subjects were less than 18 years of age at the time of Siklos® initiation and were included in the global pediatric safety set. Among them, 233 subjects were not previously treated with hydroxyurea at the time of Siklos® initiation and were included in the Safety set (SS). A total of 141 subjects had a follow-up of at least 12 months and data available to allow for biological or clinical efficacy evaluations. These subjects were included in the Efficacy Set (ES). The ESCORT-HU patient population is summarized in Table 10 below. Figure 4 illustrates the patient disposition as of the data cutoff of February 5, 2016.

Table 10. ESCORT-HU Patient Population

	# of Subjects
Total subjects enrolled at data cut-off	992
Subjects < 18 years of age (Pediatric Population)	405
Global pediatric safety set	405
Safety set (SS)	233
Efficacy set (ES)	141

Source: ESCORT-HU CSR, Synopsis

Figure 4. Patient Disposition



* Children who had previously been treated with HU prior to enrolment were those who had previously been treated with Hydrea® (which also contains HU) before Siklos initiation
FU: Follow-up; HU: hydroxyurea

Source: ESCORT-HU CSR, Section 10.1

Primary Efficacy Endpoint:
Absolute change in HbF level at least 6 months after initiation of Siklos® as compared to HbF level before initiation of Siklos®

See Section 6.1.1 for details regarding the secondary efficacy endpoints.

Duration of Treatment:
All patients were to be followed for up to 10 years. At the time of data cut-off for efficacy analysis, in the global safety set (pediatric population, N=405 patients), the mean study duration was 20.7 ± 18.6 months and the mean Siklos® treatment duration was 21.6 ± 18.5 months.

6 Review of Efficacy

Efficacy Summary

The applicant submitted the data and clinical study report to NDA 208843 in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act, on July 29, 2016 to seek approval for Siklos® (hydroxyurea) to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with recurrent moderate to severe painful crises.

The biological and clinical efficacy of Siklos® has been assessed in 141 pediatric patients with sickle cell disease 2-18 years of age, who had not been previously treated with hydroxyurea (HU) prior to enrollment in the European Sickle Cell Disease Cohort study (ESCORT-HU). Subjects had at least 12 months follow-up (median [range]: 23 months [12, 80]). Median (range) fetal hemoglobin (HbF) percentages were 5.6% (1.3, 15.0) at baseline and 12.8% (2.1, 37.2) at least 6 months after initiation of Siklos® treatment, with median (range) change of 5.9% (-2.2, 34.7) in 47 patients, and with improvement in 44 out of 47 (93.6%) patients. Median (range) hemoglobin (Hb) levels were 8.2 g/dL (3.7, 14.2) at baseline, 8.8 g/dL (0.7, 13.1) at 6 months, and 8.9 g/dL (5.5, 13.2) at 12 months after initiation of Siklos® treatment. The median (range) changes were 0.5 g/dL (-4.6, 6.1) in 63 patients at 6 months and 0.7 g/dL (-6.4, 6.0) in 83 patients at 12 months after initiation of Siklos® treatment. In total, 73 out of 83 (88.0%) patients had improvement in hemoglobin levels at 12 months after initiation of Siklos® treatment.

The results also demonstrate changes in clinical events related to sickle cell disease. When compared to the value during the 12 months prior to treatment initiation, after 12 months of treatment, there was an overall decrease in the number of subjects who experienced at least one painful crisis lasting >48 hours (from 69.2% to 42.5%), a decrease in the incidence of acute chest syndrome (from 23.6% to 5.7%), a decrease in the percentage of patients who had at least one hospitalization related to SCD (from 75.5% to 41.8%), and a decrease in the number of patients requiring transfusion (from 45.9% to 23%). However, due to concerns regarding data capture, missing data and too many zero events, the magnitude of the treatment effects is unclear.

Statistical Reviewer Comment:
Based on the data submitted, the statistical reviewer confirms that the data calculations are correct. However, we have concerns regarding the insufficient data collection and the extent of missing data based on the observational single arm study. Whether or not the observed magnitude of effect adequately captures the true effect will be based on clinical judgment.

Clinical Reviewer Comment:
Hemoglobin F (HbF) is a clinically meaningful endpoint as increases in HbF are associated with an overall improvement in the clinical manifestations of SCD, such as a decreased rate of painful vaso-occlussive crises, dactylitis and episodes of acute chest syndrome. The primary endpoint in ESCORT-HU was met and the efficacy findings are clinically significant.

6.1 Indication

The claimed indication is to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises.

6.1.1 Methods

ESCORT-HU is a multicenter, prospective, observational, cohort study in patients older than 2 years with SCD treated with Siklos® and followed-up for up to 10 years. Clinical and biological efficacy was evaluated to provide supportive data for the NDA submission to support market registration in the US for Siklos® in the pediatric population.

Primary Efficacy Endpoint:

- Absolute change in fetal hemoglobin (HbF) level at least 6 months after initiation of Siklos® as compared to HbF level before initiation of Siklos®.

Major Secondary Efficacy Endpoints:

1. Major Biological Efficacy Endpoints:
   - Absolute change in Hb level at least 6 months after initiation of Siklos® as compared to Hb level before initiation of Siklos®.
   - Absolute change in Hb level at 12 ± 2 months after initiation of Siklos® as compared to Hb level before initiation of Siklos®.

2. Major Clinical Efficacy Endpoints:
   - Proportion of patients with painful crises > 48 hours during the first year of treatment with Siklos®.
   - Absolute change in number of painful crises > 48 hours during the first year of treatment with Siklos® as compared to number of painful crises > 48 hours in the 12 months before initiation of Siklos®.
   - Proportion of patients with episodes of ACS during the first year of treatment with Siklos®.
   - Absolute change in number of episodes of ACS during the first year of treatment with Siklos® as compared to number of episodes of ACS in the 12 months before initiation of Siklos®.

- Proportion of patients with hospitalizations related to SCD during the first year of treatment with Siklos®.
- Absolute change in number of hospitalizations related to SCD during the first year of treatment with Siklos® as compared to number of hospitalizations related to SCD in the 12 months before initiation of Siklos®.
- Absolute change in number of days of hospitalizations related to SCD during the first year of treatment with Siklos® as compared to number of days of hospitalizations related to SCD in the 12 months before initiation of Siklos®.
- Proportion of patients with blood transfusions during the first year of treatment with Siklos®.

HbF evolution over time was estimated using 2 different time window definitions:

1. Wider time window: HbF after at least 6 months of Siklos® treatment was defined as the value closest to 6 months collected between 5 and 14 months.
2. Narrower time window: HbF at 6 months was defined as the value closest to 6 months collected between 5 and 7 months.

Hb evolution over time was estimated using different time window definitions:

1. Wider time window: Hb after at least 6 months of Siklos® treatment was defined as the value closest to 6 months collected between 5 and 14 months.
2. Narrower time window: Hb at 6 months of Siklos® treatment was defined as the value closest to 6 months collected between 5 and 7 months.
3. Hb after 12 months of Siklos® treatment was defined as the value closest to 12 months collected between 10 and 14 months.

Statistical Reviewer Comment:
The definition of the assessment windows for HbF and Hb were artificially extended by the Applicant. Details of the discussion are presented in section 6.1.4: Analysis of Primary endpoints.

Analysis Population

Efficacy set: The primary efficacy population was the efficacy set defined as patients who were not previously treated with HU, had at least 12 months follow-up, and had data allowing for biological or clinical efficacy evaluations.

Safety set: The primary safety population was the safety set defined as patients who were not previously treated with HU.

Overall, 992 patients were enrolled in the ESCORT-HU study. Of these, 405 of them were less than 18 years old at the time of HU initiation and were included in the Global Safety Set. Among them, 233 patients were not previously treated with HU prior to enrolment and were included in the Safety Set. A follow-up of at least 12 months and data allowing biological or clinical efficacy evaluations were available for 141 subjects.

The data cutoff was February 5, 2016.

The patient disposition graph is shown in Section 5.3 (Figure 4).

Efficacy Analysis for Primary and Secondary Biological Endpoints (HbF and Hb):
Continuous data were summarized using the number of observations, mean, 95% confidence interval (CI) of the mean, standard deviation (SD), median, 25% and 75% percentiles, minimum and maximum. Quantitative data was compared before and after initiation of Siklos® using the paired Student t-test (normal variable) or the Wilcoxon sign-rank test (non-normal data).

***Statistical Reviewer Comment**:*
It is not acceptable to include the inferential results from the biological efficacy endpoints, HbF and Hb in the label because of the concern regarding inadequate data collection and the extensive missing data. It is acceptable to include the raw data with median values in the label. However, p-values should not be included. A discussion of data adequacy is included in section 6.1.4: Analysis of Primary Endpoint, and section 6.1.10: Additional Efficacy Issues/Analyses.

Sensitivity Analyses for Primary and Secondary Biological Endpoints (HbF and Hb):
Sensitivity analyses for HbF and Hb were conducted by computing the mean value of all measures obtained in the time windows according to the worst case scenario (lowest measure of HbF or Hb).

Missing data Handling Strategies and Supportive Analyses:
Missing data were not managed or replaced. To evaluate whether the patient subgroups with missing HbF or Hb are comparable to those without missing data, baseline characteristics of patients with missing HbF or Hb both at baseline and 6 months after initiation of Siklos® were compared to those of patients without missing HbF or Hb within the efficacy set.

Major Secondary Clinical Efficacy Analyses:
Categorical data were summarized with frequencies, percentages and their 95% CI. Percentages were calculated on the overall non-missing observations. All statistical tests were 2-sided at a 5% significance level. Categorical data (%) was compared before and after initiation of Siklos® by means of the McNemar test.

Statistical Reviewer Comment:
There is no pre-specified multiplicity adjustment procedure.

6.1.2 Demographics

The efficacy dataset includes 141 patients, which were derived from the ESCORT-HU safety cohort. All patients in the efficacy set have at least 12 months of follow-up and available data for clinical and/or efficacy evaluation. Among them, 66 (46.8%) patients were male and 75 (53.2%) patients were female. Patient age ranged from 1 to 18 years. The mean (± SD) age was 8.08 ± 3.88 years, and 72.7% of patients were aged between 2 and 10 years. Race information was not collected because of EU regulations. The summary of the demographic information is presented in Table 11 below.

Table 11. Summary of Demographic Characteristics (Efficacy Set)

Demographic	***Efficacy set*** *(N=141)*
Sex	
Male	66 (46.8%)
Female	75 (53.2%)
Age	
Mean years (SD)	8.08 (3.88)
Min, max (years)	(1.3, 17.6)
≥ 2 and < 10 years	103 (73%)
≥ 10	38 (2%)
Race[1]	
	NA
Region (optional)	
United States	0 (%)
Rest of the World	141 (100%)

[1] Data on race and/or ethnicity were not collected because of local regulations
Source: FDA Statistical Reviewer

The reason for hydroxyurea initiation is presented in the table below. The most common reasons for treatment initiation were painful crisis and acute chest syndrome.

Table 12. Reason for Hydroxyurea Initiation

	Global Safety Set N=405	**Safety Set N=233**	**Efficacy Set N=141**
Previous painful crisis	248 (62.2%)	136 (59.1%)	83 (59.3%)
Acute chest syndrome	63 (15.8%)	33 (14.3%)	24 (17.1%)
Anemia	37 (9.3%)	26 (11.3%)	12 (8.6%)
Abnormal TCD	21 (5.3%)	17 (7.4%)	14 (10.0%)
Cerebral vasculopathy	11 (2.8%)	3 (1.3%)	3 (2.1%)
Sickle cell organopathy	10 (2.5%)	10 (4.3%)	2 (1.4%)
Blood transfusion issues	3 (0.8%)	3 (1.3%)	1 (0.7%)
Priapism	2 (0.5%)	0 (0.0%)	0 (0.0%)

Source: ESCORT-HU CSR

6.1.3 Subject Disposition

The first patient was enrolled on January 21, 2009 (first patient first visit) and the cut-off date for the efficacy analysis was February 5, 2016. Although a total of 49 centers were initiated in 4 countries (France, Germany, the UK, and Greece), all of the pediatric patients in the efficacy set were recruited from France (40 centers) or Germany (6 centers). Detail of the subject disposition is shown in Figure 4 (Section 5.3).

6.1.4 Analysis of Primary Endpoint(s)

For the wider time window (closest to 6 months collected between 5 and 14 months; N=47/141, 33%), the median (range) of baseline value of HbF was 5.6% (1.3, 15.0) and the median (range) of post-baseline value was 12.8% (2.1, 37.2), with a median (range) increase of 5.9% (-2.2, 34.7). Summaries of the primary efficacy analyses and sensitivity analyses are presented in the Table 13 below.

For the narrower time window (N=18/141, 13%), the median (range) of baseline value of HbF was 6.4% (1.3, 15.0) and the median (range) post-baseline value was 14.6% (5.8, 30.2), with a median (range) increase of 5.7% (-2.2, 24.2).

Statistical Reviewer Comment:
When using the narrower time window, the sample size is smaller and the missing data rate is higher (87%) than when using the wider time window (missing data rate = 67%).

Sensitivity analysis results for median reduction in HbF appear to be supportive of the results from the primary analyses.

Missing data were not managed or replaced. Baseline characteristics of patients with missing HbF or Hb both at baseline and 6 months after initiation of Siklos® were compared to those of patients without missing HbF or Hb within the efficacy set. No statistical significance was found between patients with and without Hb data for all of the parameters described, except for some variables, such as G6PD deficiency, neonatal screening, and alpha gene defects.

Table 13. Summary of Fetal Hemoglobin (HbF) After ≥6 Months of Siklos® Treatment (Efficacy Set)

		Baseline value	Post-baseline value	Changes from baseline
Fetal hemoglobin (%)				
Over 6 months (between 5 and 14 months)[a]		N=47	N=47	N=47
	Mean ± SD	6.25 ± 3.34	14.26 ± 8.52	8.01 ± 8.38[cc]
	Median (Q1 ; Q3)	5.6 (3.9 ; 7.9)	12.8 (7.1 ; 19.0)	5.9 (1.5 ; 11.9)
	Range	1.3 ; 15.0	2.1 ; 37.2	-2.2 ; 34.7
At 6 months (between 5 and 7 months)[b]		N=18	N=18	N=18
	Mean ± SD	6.74 ± 3.45	14.22 ± 6.63	7.48 ± 6.62[c]
	Median (Q1 ; Q3)	6.4 (5.0 ; 8.1)	14.6 (8.6 ; 17.7)	5.7 (4.5 ; 11.7)
	Range	1.3 ; 15.0	5.8 ; 30.2	-2.2 ; 24.2
Sensitivity analysis over 6 months				
Average of all values		N = 47	N = 47	N = 47
	(Mean ± SD)	6.25 ± 3.34	14.38 ± 8.47	8.13 ± 8.12[c]
	Median (Q1 ; Q3)	5.6 (3.9 ; 7.9)	13.5 (8.0 ; 21.3)	6.2 (-1.7 ; 34.7)
	Range	1.3 ; 15.0	2.1 ; 37.2	-1.7 ; 34.7
Worst case values		N = 47	N = 47	N = 47
	(Mean ± SD)	6.25 ± 3.34	13.58 ± 8.28	7.33 ± 8.02[c]
	Median (Q1 ; Q3)	5.6 (3.9 ; 7.9)	12.3 (7.0 ; 19.0)	5.9 (1.4 ; 11.9)
	Range	1.3 ; 15.0	2.1 ; 37.2	-2.2; 34.7
Sensitivity analysis at 6 months (Mean ± SD)				
Average of all values	Average of all values	N=18	N=18	N=18
	(Mean ± SD)	6.74 ± 3.45	14.22 ± 6.63	7.48 ± 6.62[c]
	Median (Q1 ; Q3)	6.4 (5.0 ; 8.1)	14.6 (5.8 ; 30.2)	5.7 (4.5 ; 11.7)[c]
	Range	1.3 ; 15.0	5.8 ; 30.2	-2.2 ; 24.2
Worst case values	Worst case values	N=18	N=18	N=18
	(Mean ± SD)	6.74 ± 3.45	14.22 ± 6.63	7.48 ± 6.62[c]
	Median (Q1 ; Q3)	6.4 (5.0 ; 8.1)	14.6 (8.6 ; 17.7)	5.7 (4.5 ; 11.7)
	Range	1.3 ; 15.0	5.8 ; 30.2	-2.2 ; 24.2

Source: ESCORT-HU CSR, Table 11-1

All biological and clinical endpoint assessments are based on data collected from the medical record of the patient. As per study protocol, patients are evaluated at inclusion and then every 1 to 4 months in accordance with standard clinical monitoring of the disease. Events reported during the relevant period (including events reported during the year before the initiation of Siklos®) were assessed based on all information reported in the medical record. A summary of the study assessments for HbF is provided in Table 14 below.

Table 14. Number of Post-Baseline Assessments of HbF

		Efficacy Set (N=141)
At least 3 months	n	51
	Median (Min, Max)	2 (1, 4)
At least 6 months	n	47
	Median (Min, Max)	1 (1, 3)
At least 9 months	n	40
	Median (Min, Max)	1 (1, 3)
12 months	n	33
	Median (Min, Max)	1 (1, 2)

Source: FDA Statistical Reviewer

Statistical Reviewer Comments:
With at least 67% of the HbF assessments missed, it is not clear whether the patients with non-missing HbF values can adequately represent the patients with missing HbF values. To evaluate the comparability of the baseline characteristics, the applicant summarized some important baseline characteristics between patients with missing HbF vs. Patients without missing HbF (see table in section 6.1.10). In general, most of the baseline characteristics appear to be comparable. However, the Agency noticed that the following three baseline characteristics are not comparable: G6PD deficiency, alpha gene defects and neonatal screening.

Whether the incomparable findings in these variables will have any impact on the study results from HbF data will be deferred to clinical judgment.

It is noted that the median number of post-baseline assessments for HbF is just 1-2 in each 3-month interval. Due to the concern regarding inadequate data capture, which resulted in the wider window used (i.e. 5-14 months), the actual magnitude of the effect for the change from baseline in HbF is not clear.

6.1.5 Analysis of Secondary Endpoints(s)

Hemoglobin (Hb) results at least 6 months (i.e. the value closest to 6 months collected between 5 and 7 months) and 12 months (i.e. the value closest to 12 months collected between 10 and 14 months) after initiation of Siklos® treatment were presented as a secondary biological efficacy endpoint (see Table 15 below). Median (range) hemoglobin level was 8.2 g/dL (3.7, 14.2) at baseline, 8.8 g/dL (0.7, 13.1) at 6 months, and 8.9 g/dL (5.5, 13.2) at 12 months after initiation of Siklos® treatment. The median (range) change was 0.5 g/dL (-4.6, 6.1) in 63 patients at 6 months and 0.7 g/dL (-6.4, 6.0) in 83 patients at 12 months after initiation of treatment with Siklos®.

Table 15. Hemoglobin After ≥6 Months and ≥12 Months of Siklos® Treatment (Efficacy Set)

		Baseline value	Post-baseline value	Changes from baseline
Hemoglobin (g/dL)				
After at least 6 months (between 5 and 14 months)[a]		N=106	N=106	N=106
	Mean ± SD	8.34 ± 1.51	8.82 ± 1.56	0.47 ± 1.56[d]
	Median (Q1 ; Q3)	8.2 (7.3 ; 9.2)	8.9 (7.9 ; 9.8)	0.5 (-0.2 ; 1.3)
	Range	3.7 ; 14.2	0.7 ; 13.1	-6.4 ; 6.1
At 6 months (between 5 and 7 months)[b]		N=63	N=63	N=63
	Mean ± SD	8.35 ± 1.51	8.76 ± 1.73	0.41 ± 1.49[e]
	Median (Q1 ; Q3)	8.2 (7.4 ; 9.3)	8.8 (7.9 ; 9.9)	0.5 (-0.4 ; 1.0)
	Range	3.7 ; 12.4	0.7 ; 13.1	-4.6 ; 6.1
At 12 months (between 10 and 14 months)[c]		N=83	N=83	N=83
	Mean ± SD	8.35 ± 1.56	8.94 ± 1.25	0.58 ± 1.59[d]
	Median (Q1 ; Q3)	8.2 (7.3 ; 9.2)	8.9 (8.2 ; 9.6)	0.7 (-0.2 ; 1.4)
	Range	3.7 ; 14.2	5.5 ; 13.2	-6.4 ; 6.0

Source: ESCORT-HU CSR, Table 11-2.

All biological and clinical endpoint assessments are based on data collected from the medical record of the patient. As per the ESCORT-HU study protocol, patients are evaluated at baseline and then every 1 to 4 months in accordance with standard clinical monitoring of the disease. Events reported during the relevant period (including events reported during the year before the initiation of Siklos®) were assessed based on all information reported in the medical record.

A summary of the hemoglobin assessments collected is provided in the Table below.

Table 16. Number of Post-Baseline Assessments of Hemoglobin (Hb)

		Efficacy Set (N=141)
At least 3 months	n	110 (78.0%)
	Median (Min, Max)	3 (1, 12)
At least 6 months	n	106 (75.2%)
	Median (Min, Max)	2 (1, 10)
At least 9 months	n	99 (70.2%)
	Median (Min, Max)	1 (1, 7)
12 months	n	83 (58.9%)
	Median (Min, Max)	1 (1, 7)

Source: FDA Statistical Reviewer's Analysis

Statistical Reviewer Comment:
Due to the concern of inadequate data capture and the extensive missing data, the magnitude of the change from baseline in Hb is not clear.

Analysis of Clinical Endpoints
Comparisons were made between the occurrence of SCD events that occurred in the 12 months prior to Siklos® treatment initiation and those events occurring within the first 12 months of treatment. This data is summarized in Table 17 below.

Painful Crisis
Data regarding the incidence of painful crisis both before and after Siklos® treatment initiation were available for 120 patients. Of these, 83 (69.2%) patients had at least one painful crisis in the 12 months prior to starting treatment with Siklos®. This number was reduced to 51 patients (42.5%) who experienced at least one painful crisis during the first year of treatment. The median (range) of painful crises before treatment initiation was 2 (0, 10), and the median (range) over the 12 months of follow up was 0 (0, 7), resulting in a change of -1 (-10, 5).

Acute Chest Syndrome
Data regarding the incidence of acute chest syndrome (ACS) both before and after Siklos® treatment initiation were available for 123 patients. Of these, 29 (23.6%) patients had at least one episode of ACS in the 12 months prior to starting treatment with Siklos®. This number was reduced to 7 (5.7%) patients who experienced ACS during the first year of treatment. The median (range) of ACS episodes before treatment initiation was 0 (0, 2), and the median (range) for the 12 months of follow-up was 0 (0, 1), resulting in a change of 0 (-2, 1).

Hospitalizations
Data regarding the number of patients who were hospitalized for SCD-related events both before and after Siklos® treatment initiation were available for 110 patients. Of

these, 83 (75.5%) patients had at least one hospitalization related to SCD in the 12 months prior to starting treatment with Siklos®. This number was reduced to 46 (41.8%) patients who were hospitalized during the first year of treatment. The median (range) of hospitalizations related to SCD before treatment initiation was 2 (0, 6), and the median (range) over the 12 months of follow-up was 0 (0, 7), resulting in a change of -1 (-6, 6).

Days of Hospitalization for SCD Events

Data regarding the number of days of hospitalization for SCD-related events both before and after Siklos® treatment initiation were available for 100 patients. The median (range) number of days of hospitalization related to SCD in the 12 months prior to treatment initiation was 8 (0, 58), and the median number of days of hospitalization related to SCD during the first 12 months of treatment was 0 (0, 100), resulting in a decrease of 3 days (-58, 86).

Transfusions

Data regarding the number of patients receiving at least 1 transfusion both before and after Siklos® initiation were available for 122 patients. Of these, 56 (45.9%) patients had at least one blood transfusion in the 12 months prior to starting treatment with Siklos®. This number was reduced to 28 (23.0%) patients who had at least one transfusion during the 12 months of follow-up.

Table 17. Comparison of SCD Events in the First 12 Months of Siklos® Treatment vs. SCD Events in the 12 Months Prior to Study Enrollment (Efficacy Set)

		Value during the 12 months prior to enrolment	Value during the first year of treatment with Siklos	Change Pre-Post
At least one painful crisis > 48 hours[a]		N=120	N=120	
	Yes	83 (69.2%)	51 (42.5%)	
Number of painful crises > 48 hours[b]		N=113	N=113	N=113
	Mean ± SD	2.16 ± 2.12	0.81 ± 1.31	-1.35 ± 2.15
	Median (Q1 ; Q3)	2.0 (0.0 ; 3.0)	0.0 (0.0 ; 1.0)	-1.0 (-3.0 ; 0.0)
	Range	0.0 ; 10.0	0.0 ; 7.0	-10.0 ; 5.0
	Missing	10	1	10
At least one episode of acute chest syndrome[a]		N=123	N=123	
	Yes	29 (23.6%)	7 (5.7%)	
Number of episodes of acute chest syndrome[b]		N=123	N=123	N=123
	Mean ± SD	0.26 ± 0.51	0.06 ± 0.23	-0.20 ± 0.53
	Median (Q1 ; Q3)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)
	Range	0.0 ; 2.0	0.0 ; 1.0	-2.0 ; 1.0
At least one hospitalization related to SCD[a]		N=110	N=110	
	Yes	83 (75.5%)	46 (41.8%)	
Number of hospitalizations related to SCD[b]		N=106	N=106	N=106
	Mean ± SD	1.97 ± 1.70	0.86 ± 1.34	-1.11 ± 1.84
	Median (Q1 ; Q3)	2.0 (0.0 ; 3.0)	0.0 (0.0 ; 1.0)	-1.0 (-2.0 ; 0.0)
	Range	0.0 ; 6.0	0.0 ; 7.0	-6.0 ; 6.0
Number of days of hospitalization related to SCD[b]		N=100	N=100	N=100
	Mean ± SD	11.64 ± 13.52	5.23 ± 11.86	-6.41 ± 16.34
	Median (Q1 ; Q3)	8.0 (0.0 ; 16.0)	0.0 (0.0 ; 7.5)	-3.0 (-12.5 ; 0.0)
	Range	0.0 ; 58.0	0.0 ; 100.0	-58.0 ; 86.0
At least one transfusion		N=122	N=122	
	Yes	56 (45.9%)	28 (23.0%)	

Source: ESCORT-HU CSR, Table 11-4.

A summary of the occurance of study assessments for clinical events is provided in the tables below.

Table 18. Number of Post-Baseline Assessments of Painful Crises > 48 Hours

		Efficacy Set (N=141)
At least 3 months	n	65 (46.1%)
	Median (Min, Max)	1 (1, 7)
At least 6 months	n	90 (63.8%)
	Median (Min, Max)	2 (1, 10)
At least 9 months	n	104 (73.8%)
	Median (Min, Max)	2 (1, 12)
12 months	n	113 (92.9%)
	Median (Min, Max)	3 (1, 15)

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

Table 19. Number of Post-Baseline Assessments of Episodes of ACS

		Efficacy Set (N=141)
At least 3 months	n	75 (53.2%)
	Median (Min, Max)	2 (1, 7)
At least 6 months	n	100 (70.9%)
	Median (Min, Max)	2 (1, 10)
At least 9 months	n	114 (80.9%)
	Median (Min, Max)	2 (1, 12)
12 months	n	123 (87.2%)
	Median (Min, Max)	3 (1, 15)

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

Table 20. Number of Post-Baseline Assessments of Hospitalizations Related to SCD

		Efficacy Set (N=141)
At least 3 months	n	57 (40.4%)
	Median (Min, Max)	1 (1, 9)
At least 6 months	n	83 (58.9%)
	Median (Min, Max)	2 (1, 12)
At least 9 months	n	95 (67.4%)
	Median (Min, Max)	2 (1, 14)
12 months	n	106 (75.2%)
	Median (Min, Max)	3 (1, 35)

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

Statistical Reviewer Comments:
Due to many zero events in these clinical endpoints (58%, 94%, 58% and 77% zero event rates for >1 painful crisis, > 1 episode of acute chest syndrome, >1 hospitalization and >1 transfusion, respectively), the count data may be over dispersed. The summaries of results based on mean (±SD) may be problematic. A more appropriate analysis may be based on the annualized rate using a method such as zero inflated negative binomial approach.

Due to the concerns regarding inadequate data capture, extensive missing data and questionable summary statistics, the magnitude of the change in various clinical assessments is not clear.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Subgroup analysis by gender and age demonstrated results that were consistent with the results from the whole efficacy set. These results are summarized in the tables below. In general, the subgroup results for HbF and Hb appear to be similar to those observed based in the primary analyses.

Table 21. Subgroup Analysis by Gender

	Male	**Female**
HbF change (%), Median (Range)		
Over 6 months (5 to 14)	5.4 (1.8, 15.0); n=22	5.5 (-2.2, 30.1); n=25
At 6 months (5 to 7)	6.8 (3.2, 12.7); n=8	5.0 (-2.2, 24.2); n=10
Hb change (g/dL), Median(Range)		
Over 6 months (5 to 14)	0.7 (-6.4, 6.1); n=47	0.5 (-1.7, 2.6); n=59
At 6 months (5 to 7)	0.7 (-4.6, 6.1); n=25	0.4 (-1.7, 2.6); n=38

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

Table 22. Subgroup Analysis by Age

	2 ≤ Age < 10	Age ≥ 10
HbF change (%), Median (Range)		
Over 6 months (5 to 14)	5.9 (-0.2, 34.7); n=35	6.4 (-2.2, 30.1); n=11
At 6 months (5 to 7)	5.9 (1.2, 24.2); n=13	4.8 (-2.2, 12.1); n=5
Hb change (g/dL), Median(Range)		
Over 6 months (5 to 14)	0.5 (-6.4, 6.1); n=75	0.6 (-4.6, 2.6); n=29
At 6 months (5 to 7)	0.5 (-1.7, 6.1); n=46	0.1 (-4.6, 2.3); n=17

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

Missing Data

One issue with Study ESCORT-HU is the high missing data rate (87% missing based on narrow assessment window, and 67% missing based on wide assessment window) in the primary efficacy endpoint, HbF.

To evaluate the comparability between patients with missing HbF and patients with non-missing HbF, patient characteristics assessed both at baseline and 6 months after initiation of Siklos® were compared. A summary of this comparison is presented in the Table 23 below. In general, most characteristics appear to be comparable, with the exception of G6PD deficiency, alpha gene defects and neonatal screening. Whether or not these observed differential baseline characteristics will have any impact on the interpretation of the HbF results will be deferred to clinical judgment.

Table 23. Baseline Differences in Patient Subgroups with HbF Missing and Non-Missing

Variables		Missing HbF (n=94)	Non-Missing (n=47)	P-value
Sex	n	94	47	
	Male	44 (46.8%)	22 (46.8%)	1.000
	Female	50 (53.2%)	25 (53.2%)	
Age (years)	n	94	47	
	Mean ± SD	8.5 ± 3.9	7.3 ± 3.7	0.103
Age (years) – Categorical	n	93	46	
	2-10	66 (71.0%)	35 (76.1%)	0.324
	>10-16	22 (23.7%)	11 (23.9%)	
	>16	5 (5.4%)	0	
	Missing	1	1	
Height (cm)	n	82	28	
	Mean ± SD	127.9 ± 21.0	120.5 ± 19.4	0.141
Weight (kg)	n	89	30	
	Mean ± SD	27.7 ± 12.4	23.6 ± 7.7	0.198
Physical Exam	n	66	28	
	Normal	39 (59.1%)	15 (53.6%)	0.621
	Abnormal	27 (40.9%)	13 (46.4%)	
	Missing	28	19	
Medical History				
Growth delay	n	86	47	
	No	79 (91.9%)	45(95.7%)	0.492
	Yes	7 (8.1%)	2 (4.3%)	
	Missing	8	0	
Renal impairment	n	94	47	
	No	93 (98.9%)	47 (100.0%)	1.000
	Yes	1 (1.1%)	0	
Hepatic impairment	n	93	47	
	No	90 (96.8%)	47 (100%)	0.551
	Yes	3 (3.2%)	0	
	Missing	1	0	
Cardiac impairment	n	94	47	
	No	90 (95.7%)	46 (97.9%)	0.665
	Yes	4 (4.3%)	1 (2.1%)	

Malaria	n	51	25	
	No	51 (100%)	24 (96.0%)	0.329
	Yes	0	1 (4.0%)	
	Missing	43	22	
Tuberculosis	n	52	26	
	No	52 (100%)	25 (96.2%)	0.333
	Yes	0	1 (3.8%)	
	Missing	42	21	
G6PD deficiency	N	57	40	
	No	44 (77.2%)	38 (95.0%)	0.017
	Yes	13 (22.8%)	2 (5.0%)	
	Missing	37	7	
Does the patient present any other genetic disorder?	n	67	44	
	No	57 (85.1%)	42 (95.5%)	0.120
	Yes	10 (14.9%)	2 (4.5%)	
	Missing	27	3	
Malignancies	n	94	47	
	No	94 (100%)	47 (100%)	
	Yes	0	0	
Other relevant disease	n	94	47	
	No	59 (62.8%)	19 (40.4%)	0.012
	Yes	35 (37.2%)	28 (59.6%)	
History of disease				
Duration since SCD diagnosis	n	84	42	
	Mean ± SD	6.4 ± 4.2	6.6 ± 3.4	0.746
Genotype of the patient	n	91	47	
	SS	77 (84.6%)	45 (95.7%)	0.302
	SC	2 (2.2%)	0	
	Sβ0	9 (9.9%)	2 (4.3%)	
	Sβ+	3 (3.3%)	0	
	SD	0	0	
	SE	0	0	
	SO	0	0	
	Missing	3	0	
Alpha gene defects	n	66	28	
	aa/aa	8 (12.1%)	8 (28.6%)	<.001
	-a/aa	3 (4.5%)	4 (14.3%)	
	-a/-a	4 (6.1%)	1(3.6%)	
	--/aa	0	0	

	aaa/aa	0	0	
	Not tested	47 (71.2%)	14 (50.0%)	
	Other	4 (6.1%)	1 (3.6%)	
	Missing	28	19	
Duration of the first appearance of SCD symptoms (year)	n	79	42	
	Mean ± SD	6.2 ± 4.2	5.2 ± 2.9	0.373
Neonatal screening	n	70	44	
	Normal	34 (48.6%)	10 (22.7%)	0.006
	Abnormal	36 (51.4%)	34 (77.3%)	
	Missing	24	3	
SCD Events:				
Painful crisis > 48h	n	90	47	
	No	25 (27.8%)	20 (42.6%)	0.080
	Yes	65 (72.2%)	27 (57.4%)	
	Missing	4	0	
Number of crises	n	58	27	
	Mean ± SD	3.3 ± 1.9	3.6 ± 4.8	0.416
Acute chest syndrome	n	93	47	
	No	73 (78.5%)	33 (70.2%)	0.281
	Yes	20 (21.5%)	14 (29.8%)	
	Missing	1	0	
Number of episodes	n	20	14	
	Mean ± SD	1.1 ± 0.4	1.1 ± 0.4	0.792
Hospitalization related to SCD	n	89	47	
	No	23 (25.8%)	14 (29.8%)	0.623
	Yes	66 (74.2%)	33 (70.2%)	
	Missing	5	0	
Number of Hospitalization	n	62	33	
	Mean ± SD	2.4 ± 1.4	3.2 ± 1.4	0.014
Total number of days of hospitalization	n	61	29	
	Mean ± SD	15.1 ± 13.7	16.0 ± 11.9	0.479
At least one transfusion - Enrolment	n	92	47	
	No	55 (59.8%)	21 (44.7%)	0.091
	Yes	37 (40.2%)	26 (55.3%)	
	Missing	2	0	
SCD complications:				

Avascular necrosis	n	68	45	
	No	67 (98.5%)	43 (95.6%)	0.562
	Yes	1 (1.5%)	2 (4.4%)	
	Missing	26	2	
Cutaneous hypertension	n	68	45	
	No	68 (100%)	45 (100%)	
	Yes	0	0	
	Missing	26	2	
Pulmonary hypertension	n	68	45	
	No	66 (97.1%)	45 (100%)	0.516
	Yes	2 (2.9%)	0	
	Missing	26	2	
Splenic sequestration	n	68	45	
	No	53 (77.9%)	29 (64.4%)	0.115
	Yes	15 (22.1%)	16 (35.6%)	
	Missing	26	2	
Stroke	n	66	45	
	No	64 (97.0%)	45 (100%)	0.514
	Yes	2 (3.0%)	0	
	Missing	28	2	

Source: Statistical Reviewer's Assessment from Applicant's Submission

Clinical Reviewer Comments:
Baseline differences in the incidence of G6PD Deficiency, neonatal screening and alpha gene defects are unlikely to have any impact on hemoglobin F values. In general, the baseline characteristics for subjects with missing HbF and patients without missing HbF values appear similar. As such, it is reasonable to rely on the HbF findings from the ESCORT-HU study.

Data Collection
The second issue of concern is data collection. Because ESCORT-HU was an observational study, there was not a regular assessment schedule. Therefore, the data analysis is more of a post hoc analysis. It is noted that the median numbers of post-baseline assessments for both biological and clinical efficacy endpoints are no more than 3. Due to the concern of inadequate data capture and the extent of missing data, the actual magnitude of the effect for the change from baseline in these endpoints is not certain.

Supportive Studies from the Literature
For support of their application, the Applicant submitted two major published controlled studies for the same target indication as Siklos® (Ferster, Vermylen et al.1996; Jain, Sarathi et al. 2012), and three published controlled studies in pediatric patients with

SCA (Wang, Ware et al. 2011; Ware, Davis et al. 2016; Ware and Helms 2012). The primary genotypes included in the ESCORT-HU population are representative of the HbSS and HbS^0-thalassemia genotypes, with HbSS genotype present in 88.4% patients of the efficacy set. However one of these studies (Jain, Sarathi et al.) only included patients with the Indian-Arab haplotype. Differences in baseline HbF levels should be taken into account when comparing the change from baseline in this study. The three studies with the non-target population may not provide proper supportive information. The magnitude of the results from the (Ferster, Vermylen et al. 1996) study is similar to that demonstrated in the ESCORT-HU study. A summary of the efficacy results from the supportive studies provided by the Applicant is provided in the table below.

Table 24. Efficacy Summary of Supportive Studies

Study Name	HbF (%)	Hb (g/dL)
ESCORT-HU (n=141)	At least 6 mo.: +8.01 (8.38) 6.25 (3.34) to 14.26 (8.52)	At least 6 mo.: +0.47 (1.56) 8.34 (1.51) to 8.82 (1.56) At 12 mo.: +0.58 (1.59) 8.35 (1.56) to 8.94 (1.25)
Published Controlled Studies in the Target Population		
Ferster, Vermylen et al. 1996 (n=25)	+10.69 4.65 (4.81) to 15.34 (11.3)	+0.4 8.1 (0.75) to 8.5 (0.83)
Jain, Sarathi et al. 2012 (n=60)	HU: 19.80 (6.90) to 24.0 (5.90) Ctrl: 19.21(6.37) to 18.92 (5.70)	HU: 8.10 (0.68) to 9.29 (0.55) Ctrl: 8.21 (0.68) to 7.90 (0.5)
Published Controlled Studies in the Non-Target Population		
Wang, Ware et al. 2011 (n=193)	HU: -37%, 27.1 to 17.1 Ctrl: -13%, 25.6 to 22.4	HU: -7%, 9.2 to 8.6 Ctrl: +3%, 8.9 to 9.1
Ware, Davis et al. 2016 (n=121)	HU: -0.1, 10.3 (6.5) to 10.3 (7.3) Ctrl: +15.5, 8.8 (5.5) to 24.4 (7.9)	HU: -0.1, 9.3 (0.8) to 9.2 (0.7) Ctrl: -0.2, 9.2 (0.8) to 9.1 (1.1)
Ware and Helms 2012 (n=133)	HU: -0.2, 1.7 (1.0-2.5) to 1.3 (0.8-2.7) Ctrl: +17.9, 1.4 (0.8-2.2) to 19.5 (10-24.3)	HU: 0.0, 9.2 (8.6-9.7) to 9.0 (8.7-9.6) Ctrl: 0.0, 9.2 (8.5-9.6) to 9.0 (8.4-9.6)

Source: FDA Statistical Reviewer's Analysis from Applicant's Response to IR.

Labeling recommendation:

The Applicant proposed to present results from historical studies in the label. The Agency does not consider the historical study data to be adequate, considering that the study populations, study settings and endpoint assessments in those studies may not be comparable with those in the pivotal ESCORT-HU study.

Per SAP, the efficacy set (n=141) is the primary analysis set for all efficacy analyses. However, the Applicant performed the analyses using 106 and 123 subjects for biological and clinical efficacy, respectively. This does not follow the pre-specified analyses.

The Agency does not agree with the inferential results from the primary biological efficacy endpoint, HbF, because of the high missing data rate (~67%) and the concern regarding inadequate data collection. The change from baseline in HbF value should be evaluated using the median instead of the mean value due to the concern that the data may be skewed.

For the secondary clinical efficacy endpoints, the Agency does not agree that any inferential results should be included in the label due to the concern of data collection. Specifically, p-values should not be included in the label for these secondary efficacy endpoints. There was also no pre-specified multiplicity adjustment procedure. In addition, there are too many zeros in the secondary clinical efficacy endpoints, such as the number of painful crisis, number of episodes of ACS, and the number of hospitalizations related to SCD, in both prior and post-Siklos® treatment assessments. Hence, it is not appropriate to use mean values to summarize the efficacy results based on these variables. The Applicant did not collect the number of transfusions in the 12 months prior to treatment, so we are unable to compare the numbers of transfusions between pre and post treatment.

While ESCORT-HU did not collect information regarding the overall number of transfusions administered to pediatric patients receiving Siklos®, the number of subjects requiring at least 1 transfusion decreased with Siklos® use. Based on this finding, as well as extrapolation from the Droxia® efficacy findings in adults, and support from the published literature, this claim is supported.

7 Review of Safety

Safety Summary

The safety profile of Siklos® in pediatric patients with SCD is based on data from the pivotal study, ESCORT-HU, conducted in patients 2 years of age and older, as well as supportive data from published clinical studies using hydroxyurea in pediatric patients with SCD.

ESCORT-HU
At the time of data cut-off (February 5, 2016), a total of 992 subjects were enrolled. Of these, 405 subjects were less than 18 years of age at the time of Siklos® initiation and were included in the global pediatric safety set. Among them, 233 subjects were not previously treated with hydroxyurea at the time of Siklos® initiation and are included in the Safety Set (SS).

A summary of the key safety findings are listed below:

- The Siklos® starting dose was 15 mg/kg orally once daily. The dose could be increased, as tolerated, by 5 mg/kg/day every 8 weeks or if a crisis occurred, until a maximum tolerated dose or 35 mg/kg/day was reached.
- In total, 63 (15.6%) subjects in the Global Safety Set and 36 (15.5%) subjects in the Safety Set had a dose reduction due to adverse reactions or lab abnormalities. No subjects discontinued study drug due to an adverse event.
- Serious treatment-emergent adverse reactions (including both sickle-cell related events and non-sickle cell related events) were reported in 109 (26.9%) subjects in the global safety set and 63 (27.0%) subjects in the safety set.
- The most frequent non-sickle cell related serious adverse reactions in the global safety set were infections (18.0%), thrombocytopenia (3.7%) and neutropenia (3.0%).
- Additional safety issues have been identified with the use of hydroxyurea including myelosuppression, skin and subcutaneous tissue disorders, carcinogenicity and teratogenicity.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for Siklos® included the review of the following items submitted by the Applicant (Addmedica SAS).

- Clinical study report for Study ESCORT-HUProtocol and statistical analysis plan for Study ESCORT-HU
- Raw and derived datasets for Study ESCORT-HU
- Response to information requests

- Supportive published controlled studies
- Supportive published non-controlled studies
- Proposed labeling for Siklos®

7.1.2 Categorization of Adverse Events

In study ESCORT-HU, adverse events (AEs) were coded using Sponsor's internal code and classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Cumulative data was summarized using MedDRA Preferred terms (PT). The physician was required to assess causality for all AEs (serious and non-serious) and to describe the maximum intensity of the AE (mild, moderate or severe).

The safety analysis of Siklos® in the pediatric sickle cell disease population focused on adverse events not related to sickle cell disease. Sickle-related events were not routinely reported in the published controlled and non-controlled studies of hydroxyurea and are therefore not included in the Applicant's safety analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Given the differences in study designs used to support this application, no pooled data analyses were performed.

7.2 Adequacy of Safety Assessments

See section 3.1 for information regarding the data quality.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographics of the Safety Population

The pediatric safety population for ESCORT-HU is divided into the Global Safety Set (N=405) and the Safety Set (N=233). The Global Safety set includes all pediatric subjects who received at least 1 dose of Siklos®. The Safety Set is defined as the subgroup of pediatric patients not previously treated with HU prior to enrollment and age <18 years old at initiation with Siklos®. The patient demographics and baseline disease characteristics are presented in Table 25 below.

Table 25. Baseline Demographics of the Safety Populations

	Global Safety Set N (%)	Safety Set N (%)
N	405	233
Gender		
Male	207 (51.1)	112 (48.1)
Female	198 (48.9)	121 (51.9)
Age (years)		
Mean ± SD	9.65 ± 4.26	8.13± 4.17
Range	1.1;18.0	1.1;18.0
Age Category		
2-10 years	215 (53.9)	158 (69.6)
10-16 years	149 (37.3)	56 (24.7)
>16 years	35 (8.8)	13 (5.7)

Source: ESCORT-HU CSR, Section 10.4.1.

Baseline Disease and Comorbidity Characteristics of the Safety Population

The baseline disease and comorbidity characteristics for the safety populations are presented in Table 26 below.

Table 26. Baseline Disease and Comorbidity Characteristics of the Safety Populations

	Global Safety Set N (%)	Safety Set N (%)
N	405	233
Duration since SCD Diagnosis (years)		
n	369	208
Mean ± SD	8.35 ±4.51	6.72 ± 4.28
Median (Min;Max)	8.3 (0.0;17.9)	6.1 (0.0;17.6)
Missing	36	25
Genotype		
n	396	224
SS	361 (91.2)	198 (88.4)
SC	8 (2.0)	6 (2.7)
Sβ0	19 (4.8)	13 (5.8)
Sβ+	8 (2.0)	7 (3.1)
Missing	9	9
Neonatal Screening		
n	347	189
No	132 (38.0)	72 (38.1)
Yes	215 (62.0)	117 (61.9)
Missing	58	44

	Global Safety Set N (%)	Safety Set N (%)
N	405	233
SCD Events in the 12 months prior to enrollment		
Painful Crisis > 48 hrs		
n	395	225
No	165 (41.8)	84 (37.3)
Yes	230 (58.2)	141 (62.7)
Missing	10	8
If Yes: Number of Crises		
n	216	129
Mean ± SD	3.05 ± 2.97	3.21 ± 3.06
Median (Min;Max)	2.0 (1.0;27.0)	2.0 (1.0;27.0)
Missing	14	12
Acute Chest Syndrome		
n	396	225
No	325 (82.1)	182 (80.9)
Yes	71 (17.9)	43 (19.1)
Missing	9	8
If Yes: Number of episodes		
n	70	43
Mean ± SD	1.11 ± 0.36	1.14 ± 0.41
Median (Min;Max)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
Missing	1	0
Hospitalizations related to SCD		
n	395	224
No	153 (38.7)	77 (34.4)
Yes	242 (61.3)	147 (65.6)
Missing	10	9
If Yes, Number of Hospitalizations		
n	234	141
Mean ± SD	2.53 ± 1.64	2.58 ± 1.58
Median (Min; Max)	2.0 (0.0;10.0)	2.0 (0.0;10)
Missing	8	6
SCD Complications:		
Avascular necrosis	26 (6.4)	7 (3.0)
Cutaneous ulcers	0 (0.0)	0 (0.0)
Pulmonary hypertension	6 (1.5)	3 (1.3)
Splenic sequestration	81 (20.0)	53 (22.7)
Stroke	10 (2.5)	3 (1.3)

Source: ESCORT-HU CSR, Section 10.4

7.2.2 Explorations for Dose Response

The median exposure duration and cumulative exposure for the safety populations are presented in the tables below. Patients treated with Siklos® in the Global Safety Set received treatment for a median of 18 months, and patients in the Safety Set received treatment for a median of 17 months.

Table 27. Siklos® Exposure

Treatment Duration (months)	Global Safety Set N=405	Safety Set N=233
n	403	231
Duration of Exposure to Siklos®		
Mean ± SD	21.6 ± 18.5	20.2 ± 18.1
Median (Min, Max)	18 (9, 28)	17 (9, 25)

Source: ESCORT-HU CSR

In pediatric patients enrolled on ESCORT-HU, Siklos® was initiated at a mean dosage of 17.75 ± 4.41 mg/kg/day. Pediatric patients newly treated with Siklos® (Safety Set) received a mean dosage of 16.66 ± 3.95 mg/kg/day at treatment initiation. The dosage of Siklos® at the time of treatment initiation is presented in the table below.

Table 28. Dosage of Siklos® at Enrollment on ESCORT-HU

	Global Safety Set N=405	Safety Set N=233
n	399	227
Mean ± SD	17.75 ± 4.41	16.66 ± 3.95
Median (Min;Max)	17.0 (2.0;35.0)	16.0 (15.0;19.0)
Missing	6	6

Source: ESCORT-HU CSR

Of the 405 pediatric patients in the Global Safety Set, 32 had no follow-up. Therefore, exposure data are available for 373 patients. Daily dose was not reported for one patient.

Table 29 below includes information regarding the highest doses received by pediatric patients enrolled on ESCORT-HU.

Table 29. Pediatric Patients Exposed to Siklos® in ESCORT-HU (Global Safety Set, N=405)

Exposure duration	Siklos® highest daily dose (mg/kg/day) reported in CRF					Total (N=405)
	<20	20-24	25-29	30-35	>35	
No follow-up						32
< 6 months[a]	22	17	5	0	0	45[a]
≥ 6 months to < 12 months	32	35	12	2	1[b]	82
≥ 12 months to < 18 months	26	19	10	2	1[c]	58
≥ 18 months to < 24 months	23	28	14	0	0	65
≥ 24 months to < 30 months	14	22	6	0	1[d]	43
≥ 30 months to < 36 months	10	10	7	0	1[e]	28
≥ 36 months to < 42 months	0	0	1	3	1[f]	5
≥ 42 months to < 48 months	0	2	1	2	0	5
≥ 48 months	2	13	16	10	1[g]	42
Total number of patients exposed to Siklos	129	146	72	19	6	373[a]

Source: Applicant's response to IR

Limited information was provided regarding exposure, particularly after dose escalation. Datasets provided contained an extensive amount of missing data and lacked start/stop dates. Therefore, safety analyses by exposure were not able to be performed.

This data, in combination with supportive data from the literature, supports dosing up to a maximum dose of 35 mg/kg/day.

Dose Modifications

Two hundred eighty two (282) subjects (69.6%) in the global safety set and 165 subjects (70.8%) in the safety set had at least one dose modification. The majority of dose modifications were due to weight adjustments for normal weight gain. The table below depicts the number of dose modifications for patients in both safety sets.

Table 30. Siklos® Dose Modifications

	Global Safety Set N=405	Safety Set N=233
Subjects with at least 1 dose Modification	282 (69.6%)	165 (70.8%)
Adjustment due to body weight/Normal weight gain	203 (72%)	121 (73.3%)
Recurrence of VOC	97 (34.4%)	53 (32.1%)
Bone marrow intolerance	12 (4.3%)	12 (7.3%)
Toxicity	10 (3.5%)	6 (3.6%)
Patient's will	10 (3.5%)	9 (5.5%)
Other (Not Specified)	119 (42.2%)	78 (47.3%)

Source: ESCORT-HU CSR, Table 10-2

7.2.3 Special Animal and/or In Vitro Testing

Results of the relevant preclinical studies are summarized in section 4.2.

7.2.4 Routine Clinical Testing

Refer to section 5.3.1 for the schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Across the published controlled studies of hydroxyurea in pediatric patients with sickle cell disease used in support of this application, a total of 278 unique patients received hydroxyurea. At least 229 patients received hydroxyurea for 6 months or more (207 for 18 months or more). The duration of treatment ranged between 6 and 30 months. The extent of exposure in the published controlled studies is provided in Table 31 below.

Table 31. Extent of Exposure: Published Controlled Studies

	Published Controlled Study				
	Jain 2012	Ferster 1996	Wang 2011	Ware 2012; Alvarez 2013	Ware 2016
	N=60	N=25[1]	N=193	N=134	N=121
Received HU n (%)	30 (50%)	25 (100%)	96 (49.7%)	67 (50.0%)	60 (49.5%)
Manufacturer/Formulation	HU capsules	BMS Hydrea® capsules	HU liquid formulation	Not specified	HU capsules or liquid formulation
Duration of treatment available (n,%)	18 months (30, 100%)	6 months (25, 100%)	24 months (96, 100%)	30 months[3] (24, 35.8%)[2]	24 months[3] (57, 95%)
Mean±SD (range)	/	/	NR	23.4±7.4 (5.1-31.9)	NR
<6 months n (%)	0	3 (12%)	NR	NR	NR
6-12 months n (%)	0	22 (88%)	NR	NR	NR
12-24 months n (%)	30 (100%)	0	NR	NR	NR
24-36 months n (%)	0	0	NR	NR	NR
36-48 months n (%)	0	0	NR	NR	NR
>48 months n (%)	0	0	NR	NR	NR
Daily Dose (mg/kg b. w./d)	10 mg/kg/day Fixed dose	20 mg/kg/day (n=20) 25/mg/kg/day (n=5)	20 mg/kg/day Fixed dose	Starting dose: 20 mg/kg/day, then escalation until MTD (n=60, 90% reached MTD)	Starting dose: 20 mg/kg/day, then escalation until MTD (n=57, 95% reached MTD)
Median (range)	10 mg/kg/day	NR	20 mg/kg/day	27.6 (9.9-32.8) mg/kg/day	27.4 (24-30.1) mg/kg/day
Mean ±SD (SE)	10 mg/kg/day	NR	20 mg/kg/day	26.2± 4.9 mg/kg/day	NR

[1] Due to the cross-over design patients received both HU and placebo. 3 patients were excluded from the analysis after 4-5 months due to failure to attendance at monthly visits.
[2] 31% of the 134 included children were still taking HU at the 6 month follow-up visit (including treatment crossovers)
[3] including combined transfusion for 4-9 months while HU dose was escalated until MTD
Abbreviations: N: Number of patients; NR: Not reported; MTD: Maximum tolerated dose; SD: standard deviation; SE: standard error

Source: Siklos® Integrated Summary of Safety, Section 5.2.3, Table 13.

Published Controlled Studies: Overview of Safety Results

The safety profile of hydroxyurea for the treatment of adults with SCD is well established, and many studies of hydroxyurea in pediatric patients with SCD have been reported in the literature. An overall summary of all adverse events reported in the published controlled studies in pediatric patients is provided in Table 32 below. The BABY HUG, SWiTCH and TWiTCH studies reported safety data. Details of adverse events were not reported in the other two published controlled studies.

Across the 5 studies, no adverse events leading to treatment withdrawal were reported. Serious adverse events related to underlying sickle cell anemia were reported in the SWiTCH study in 32.8% and 10.6% of patients in the hydroxyurea and transfusion arms, respectively. In the TWiTCH study, serious adverse events related to underlying sickle cell anemia were reported in 15% and 10% of patients in the hydroxyurea and transfusion arms, respectively. Serious adverse events not related to underlying sickle cell disease were only reported in the SWiTCH study and occurred in 6% of patients in the hydroxyurea arm and 7.6% of patients in the transfusion arm.

Across the 5 studies, there were no adverse events that were not related to underlying sickle cell disease that resulted in death.

Table 32. Overview of Adverse Events: Published Controlled Studies

	Published Controlled Study									
	(Jain, Sarathi et al. 2012)		(Ferster, Vermylen et al. 1996)		(Wang, Ware et al. 2011)		(Ware and Helms 2012; Alvarez, Yovetich et al. 2013)		(Ware, Davis et al. 2016)	
	N=60		N=25[1]		N=193		N=134		N=121	
	HU	P	HU	P	HU	P	HU	T	HU	T
	n=30 (50%)	n=30 (50%)	n=25 (100%)	n=25 (100%)	n=96 (49.7%)	n=97 (50.3%)	n=67 (50%)	n=66[5] (49.3%)	n=60 (49.6%)	n=61 (50.4%)
All Adverse events										
Number (%) of patients with:										
At least one SCA-related AE	11 (36.7%)	30 (100%)	NR[2]	NR[2]	NR[3]	NR[3]	46 (68.7%)	44 (66.7%)	NR	NR
At least one not SCA-related AE	25 (83.3%)	30 (100%)	NR[2]	NR[2]	NR[4]	NR[4]	18 (26.9%)	20 (30.3%)	NR	NR
At least one not SCA-related severe AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (6.2%)	4 (4.1%)	NR	NR	NR	NR
At least one AE leading to withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
At least one not SCA-related AE leading to withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
At least one SCA-related SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR	22 (32.8%)	7 (10.6%)	9 (15%)	6 (9.8%)
At least one not SCA-related SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR	4 (6.0%)	5 (7.6%)	NR	NR
AE leading to Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)[6]	0 (0%)	0 (0%)
Not SCA-related AE leading to Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Individual Publications (Ferster, Vermylen et al. 1996; Wang, Ware et al. 2011; Jain, Sarathi et al. 2012; Ware and Helms 2012; Alvarez, Yovetich et al. 2013; Ware, Davis et al. 2016)
Abbreviations: AE: Adverse event; HU: Hydroxyurea; N: Number of patients; NR: Not reported; P: Placebo, SCA: Sickle cell anemia; T: Transfusion
[1] Due to the cross-over design patients received both HU and placebo. 3 patients were excluded from the analysis due to failure to attendance at monthly visits.
[2] The authors only states that no clinically relevant toxicity was associated with HU therapy
[3] The number of SCA-related events and the number of patients affected by each event is reported but not the number of patients with at least one SCA-related event
[4] The number of not SCA-related events and the number of patients affected by each event is reported but not the number of patients with at least one not SCA-related event
[5] One patient moved before starting study treatment; [6] Hemorrhagic stroke

Source: Siklos® Integrated Summary of Safety, Section 5.4.3.

Overall, the safety findings in the published controlled studies are consistent with the safety profile of Siklos® in ESCORT-HU with regards to the most frequent drug-related adverse events, i.e. blood and lymphatic disorders (neutropenia, especially in the youngest children [as seen in BABY HUG], as well as anemia, reticulocytopenia and thrombocytopenia [as seen in the SWiTCH study]), infections, gastrointestinal disorders and skin and subcutaneous tissue disorders (reported in Jain et al. 2012 and the BABY HUG studies).

7.3 Major Safety Results

Table 33. Safety Summary for Study ESCORT-HU

Event	Global Safety Set N (%)	Safety Set N (%)
N	405	233
Deaths	1 (0.2)	1 (0.4)
Serious TEAE	109 (26.9)	63 (27.0)
Permanent discontinuation due to TEAE	0 (0.0)	0 (0.0)
Treatment modification due to TEAE	63 (15.6)	36 (15.5)
Any TEAE	256 (63.2)	146 (62.7)

Source: FDA Clinical Reviewer's Analysis

7.3.1 Deaths

In the ESCORT-HU study, there was 1 death in a pediatric patient. This event was considered to be not related to Siklos® treatment.

Patient (b) (6) was a 17 year old German female with SCD (HbSS). She was enrolled in ESCORT-HU at age 12 in September, 2010, which was (b) (6) before her death. The reason for Siklos® treatment initiation was a history of painful vaso-occlusive crises. At the time of treatment initiation, the patient was noted to have a history of growth delay and hepatic impairment. Siklos® was initiated at a dose of 10 mg/kg/day daily. This was increased two months later to 20 mg/kg/day and then again two years later to 27 mg/kg/day due to recurrence of vaso-occlusive crises. In 2013, the dose was again increased to 31 mg/kg/day also due to recurrence of vaso-occlusive crises. In 2014, the dose was reduced to 23 mg/kg/day for adjustment according to patient's body weight. She underwent a bone marrow transplant on (b) (6). Post-transplant complications included hypertensive crisis, posterior reversible encephalopathy syndrome (PRES) and brain edema. Patient died (b) (6) after bone marrow transplant. No relationship with Siklos® was suspected.

7.3.2 Nonfatal Serious Adverse Events

Table 34 below depicts the non-fatal serious adverse events that were not related to underlying SCD for pediatric patients enrolled in ESCORT-HU. In the Global Safety Set, there were 176 non-SCD serious adverse events in 102 (25.2%) subjects. Of these, 4 were serious infections that were considered life-threatening. However, none of these 4 events were considered to be related to Siklos®. In the Safety Set, there were a total of 100 non-fatal serious adverse events in 60 (25.8%) subjects.

Table 34. ESCORT-HU Non-SCD-Related Serious Adverse Events

System Organ Class/ Adverse Event	Global Safety Set (n=405)	Safety Set (n=233)
Infections[1]	73 (18.0%)	42 (18.0%)
Blood and lymphatic system disorders	42 (10.4%)	18 (7.7%)
Thrombocytopenia	15 (3.7%)	5 (2.1%)
Neutropenia	12 (3.0%)	7 (3.0%)
Anemia	7 (1.7%)	4 (1.7%)
Other	7 (1.7%)	2 (0.9%)
Gastrointestinal disorders	11 (2.7%)	9 (3.9%)
Constipation	2 (0.5%)	3 (1.3%)
Nausea	2 (0.5%)	1 (0.4%)
Other	7 (1.7%)	5 (2.1%)
Nervous system disorders	11 (2.7%)	7 (3.0%)
Headache	7 (1.7%)	5 (2.1%)
Fever	6 (1.5%)	5 (2.1%)
Surgical interventions	3 (0.7%)	3 (1.3%)
Skin and subcutaneous tissue disorder	2 (0.5%)	1 (0.4%)

[1]Infections = Viral infections, Bacterial infections, Parvovirus B19, Pneumonia, Other infections
Source: FDA Clinical Reviewer's Analysis

7.3.3 Dropouts and/or Discontinuations

There were no permanent discontinuations due to non-SCD adverse events in ESCORT-HU. Permanent treatment discontinuations occurred in 24 (5.9%) pediatric patients due to:

- Loss of follow-up/move out of the study area (n=15)
- Lack of efficacy (n=1)
- Bone marrow transplantation (n=3)
- Exclusion criteria/wrongly included (n=2)

A summary of the reasons for temporarily stopping Siklos® treatment for more than 15 days is included in Table 35 below.

Table 35. Reasons for Stopping Siklos® Treatment for More Than 15 Days in Pediatric Patients Enrolled in ESCORT-HU.

Pediatric patients under 18 years	Global Safety Set N=54	Safety Set N=29
Patient's will	8 (14.8%)	6 (20.7%)
Bone marrow intolerance	6 (11.1%)	5 (17.2%)
Toxicity	5 (9.3%)	3 (10.3%)
Inefficacy	1 (1.9%)	0 (0.0%)
Recurrence of crisis	0 (0.0%)	0 (0.0%)
Other	38 (70.4%)	18 (62.1%)

Source: ESCORT-HU CSR, Table 3.3.4

7.3.4 Significant Adverse Events

7.3.4.1 Myelosuppression

Myelosuppression is the most common adverse event with hydroxyurea use. This is most likely secondary to direct inhibition of DNA synthesis by inhibition of ribonucleotide reductase thereby depleting the intracellular pool of deoxyribonucleotides (especially dATP), which induces cell cycle arrest, and impairs DNA repair.

Table 36 depicts the incidence of myelosuppression in pediatric patients enrolled in ESCORT-HU.

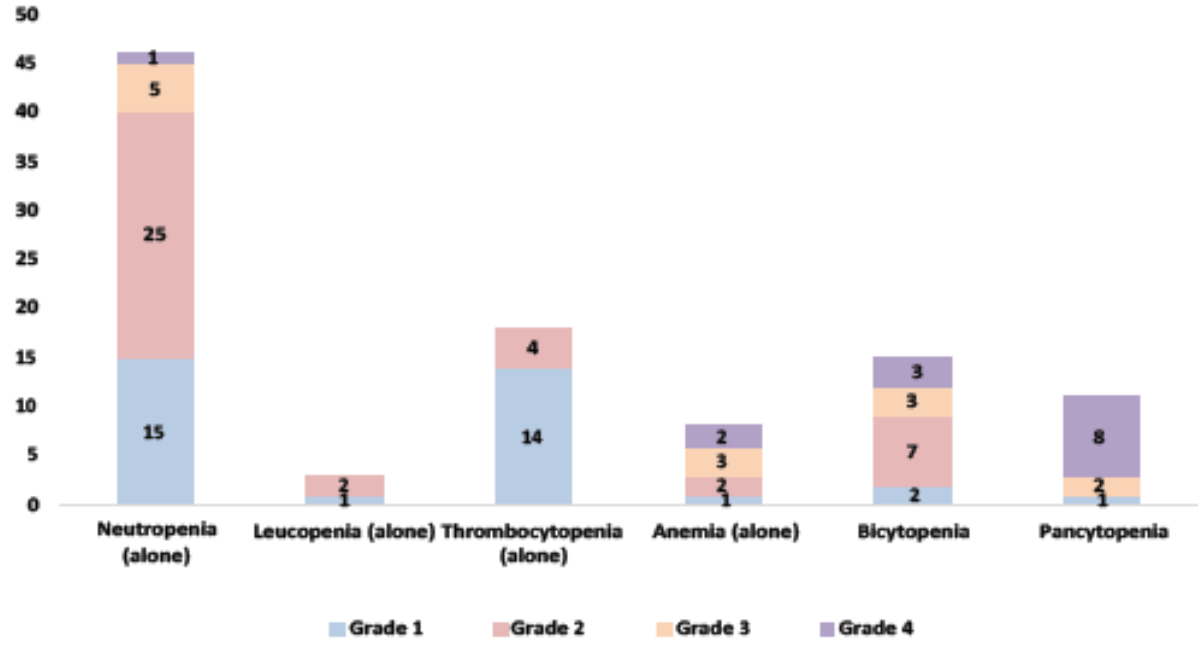
Table 36. ESCORT-HU: Incidence of Myelosuppression

	Global Safety Set (n=405)		Safety Set (n=233)	
	n	%	n	%
Neutropenia	48	11.9	31	13.3
Thrombocytopenia	23	5.7	12	5.2
Anemia	19	4.7	12	5.2

Source: FDA Clinical Reviewer's Analysis

The figure below depicts the cumulative incidence of myelosuppression, categorized by grade, from the Siklos® post-marketing safety data.

Figure 5. Siklos® Cumulative Post-Marketing Safety Data: Myelosuppression Cases by Grade



Source: Siklos® ISS. Figure 6

Neutropenia is the most common manifestation of hematological bone marrow suppression. Recovery tends to be rapid when Siklos® is discontinued, and often treatment can be resumed at a lower dose.

7.3.4.2 Skin and Subcutaneous Disorders

Leg Ulcers

Literature regarding the incidence and causality of leg ulcers in patients receiving hydroxyurea is controversial. There is some evidence that hydroxyurea may increase the incidence of cutaneous ulcerations. However, this issue is complicated by the fact that patients receiving hydroxyurea often have underlying pathological features that may make them more prone to developing skin ulcerations (i.e. sickle cell disease, thrombocytopenia, thrombosis, etc.).

As of the data cutoff, a total of nine episodes of leg ulcers have been reported in patients taking Siklos®, all in adults, with the exception of one patient, a 17 year-old male. The proposed labeling includes a caution in patients with leg ulcers, and instructions to discontinue Siklos® or to reduce the dose if cutaneous vasculitic ulcerations occur.

Other Skin Disorders

Non-ulcerative skin disorders have been reported with hydroxyurea use in both adults and children. These disorders include hyperpigmentation, nail discoloration, alopecia, and dry skin.

The Table below depicts the incidence of skin and subcutaneous tissue disorders in pediatric subjects enrolled on ESCORT-HU.

Table 37. ESCORT-HU: Incidence of Skin and Subcutaneous Disorders

	Global Safety Set (n=405)		Safety Set (n=233)	
	n	%	n	%
Skin and subcutaneous tissue disorders	32	7.9	23	9.9
Skin reactions	11	2.7	7	3.0
Cutaneous Dryness	6	1.5	6	2.6
Alopecia	1	0.2	1	0.4
Leg Ulcer	1	0.2	1	0.4
Other Skin and subcutaneous disorders	9	2.2	8	3.4

Source: FDA Clinical Reviewer's Analysis

7.3.4.3 Carcinogenicity

See section 7.6.1

7.3.4.5 Male Fertility Impairment

See section 7.6.2

7.3.5 Submission Specific Primary Safety Concerns

Refer to section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 1,225 adverse events were reported in 277 (68.4%) of pediatric patients included in the Global Safety Set (N=405), and 738 adverse events were reported in 157 (67.4%) of pediatric patients in the Safety Set. Table 38 below depicts the most common treatment-emergent adverse events of any grade.

Table 38. ESCORT-HU: Treatment-Emergent Adverse Events of Any Grade

Preferred Term N (%)	**Global Safety Set N=405**	**Safety Set N=233**
Painful episode	94 (23.2)	55 (23.6)
Neutropenia	48 (11.9)	31 (13.3)
Bacterial Infections	42 (10.4)	30 (12.9)
Viral Infections	39 (9.6)	31 (13.3)
Fever	33 (8.1)	29 (12.4)
Vitamin D Deficiency	27 (6.7)	22 (9.4)
Headache	24 (5.9)	15 (6.4)
Other Infection	23 (5.7)	14 (6.0)
Thrombocytopenia	23 (5.7)	12 (5.2)
Rash	23 (5.7)	11 (4.7)
Abdominal Pain	19 (4.7)	15 (6.9)
Anemia	19 (4.7)	12 (5.2)
Rhinitis	17 (4.2)	12 (5.2)
Pneumonia	17 (4.2)	11 (4.7)
Cholecystitis	16 (4.0)	6 (2.6)
Constipation	15 (3.7)	12 (5.2)
Pharyngitis	15 (3.7)	12 (5.2)
Parvovirus B19 Infection	12 (3.0)	9 (3.9)
Vomiting	11 (2.7)	8 (3.4)

Source: FDA Clinical Reviewer's Analysis

Non-Sickle Cell Related Adverse Events

A total of 789 non-SCD related adverse events were reported in 256 (63.2%) of pediatric patients included in the Global Safety Set (N=405), and 490 non-SCD related adverse events were reported in 146 (62.7%) of pediatric patients in the Safety Set (N=233). Table 39 below depicts the treatment-emergent non-SCD adverse events that were reported in ≥5% of subjects, summarized by preferred term.

Table 39. ESCORT-HU: Non-SCD Treatment-Emergent Adverse Events of Any Grade in ≥5% of Subjects

Preferred Term N (%)	Global Safety Set (N=405)	Safety Set (N=233)
Bacterial Infections	42 (10.4)	30 (12.9)
Neutropenia	45 (11.1)	30 (12.9)
Viral Infections	39 (9.6)	31 (13.3)
Fever	33 (8.1)	29 (12.4)
Thrombocytopenia	23 (5.7)	12 (5.2)
Rash	23 (5.7)	11 (4.7)
Headache	23 (5.7)	14 (6.0)
Vitamin D Deficiency	21 (5.2)	16 (6.9)
Rhinitis	17 (4.2)	12 (5.2)
Anemia	16 (4.0)	12 (5.2)
Pharyngitis	15 (3.7)	12 (5.2)
Constipation	15 (3.7)	12 (5.2)

Source: FDA Clinical Reviewer's Analysis

The following treatment-emergent adverse events graded as "moderate" or "severe" were reported in ≥ 2% of subjects.

Table 40. Treatment-emergent AEs Graded "Moderate" or "Severe" in ≥2% of Subjects

Preferred Term N (%)	Global Safety Set N=405	Safety Set N=233
Bacterial Infections	33 (8.2)	19 (8.2)
Neutropenia	27 (6.7)	21 (9.0)
Other Infections	17 (4.2)	10 (4.3)
Thrombocytopenia	11 (2.7)	5 (2.2)
Viral Infections	11 (2.7)	5 (2.2)
Fever	10 (2.5)	8 (3.4)
Vitamin D deficiency	7 (1.7)	5 (2.2)
Headache	6 (1.5)	5 (2.2)
Constipation	5 (1.2)	7 (3.0)

Source: FDA Clinical Reviewer's Analysis

Safety Summary for Study OTL-001-01 (Pediatric Subjects)
In the 12 pediatric subjects enrolled on this study, there were two adverse events reported in two patients. One patient developed a pulmonary infection and one developed anemia (Hb 4.9 g/dL, decreased from 5.4 g/dL prior to study treatment). Both events were classified as serious and as not related to the study medication. There were no deaths on this study.

7.4.2 Laboratory Findings

In Study ESCORT-HU, laboratory assessments were collected at baseline and at each follow-up visit, as per standard-of-care.

Per the Applicant, in ESCORT-HU, no significant changes in blood chemistry (AST, ALT, total bilirubin, direct bilirubin, GGT, LDH, creatinine, uric acid, alkaline phosphatase) and urinalysis parameters occurred with the use of Siklos®.

Analysis of laboratory findings was limited by the poor quality of the laboratory datasets. There was a significant amount of missing data and no reference ranges were provided.

The following post-baseline through post last dose laboratory abnormalities of any grade were reported in ≥1% of pediatric subjects in Study ESCORT-HU.

Table 41. ESCORT-HU: Laboratory Abnormalities of Any Grade in ≥1% of Subjects

Laboratory Parameter N (%)	Global Safety Set N=405	Safety Set N=233
Neutropenia (ANC)	45 (11.1)	30 (12.9)
Thrombocytopenia	23 (5.7)	12 (5.2)
Decreased Vitamin D	21 (5.2)	16 (6.9)
Hemoglobin Decreased	9 (2.2)	6 (2.6)
AST/ALT Increased	5 (1.2)	2 (0.9)

Source: FDA Clinical Reviewer's Analysis

7.4.3 Vital Signs

In Study ESCORT-HU, height and weight were collected at baseline and at each follow up visit. Additional vital sign parameters were not collected or summarized for study ESCORT-HU.

7.4.4 Electrocardiograms (ECGs)

ECGs were not routinely collected as part of ESCORT-HU.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No evaluations were conducted evaluating the dose dependency of adverse events because of the overall poor quality of the datasets provided and large amount of missing data.

7.5.2 Time Dependency for Adverse Events

Because of the poor data quality and extensive missing data, no conclusions were made regarding the time to onset of adverse events or the duration of events.

7.5.3 Drug-Demographic Interactions

The most frequent non-sickle cell related adverse events and relative risks categorized by age category are provided in the Table below.

Table 42. ESCORT-HU: Most Frequent Non-SCD-related Adverse Events and Relative Risks by Age Category

	[2-10 years] (N=193)	]10-16 years] (N=137)	>16 years (N=462)	RR [CI 95%] [2-10 years] versus Age in >16 years	RR [CI 95%]]10-16 years] versus Age in >16 years
Bacterial Infections	28 (14.5%)	15 (10.9%)	53 (11.5%)	1.26 [0.83, 1.94]	0.95 [0.56, 1.64]
Other Infections	38 (19.7%)	17 (12.4%)	21 (4.5%)	4.33 [2.61, 7.18]	2.73 [1.48, 5.03]
Headache	3 (1.6%)	10 (7.3%)	49 (10.6%)	0.15 [0.05, 0.46]	0.69 [0.36, 1.32]
Viral Infections	16 (8.3%)	8 (5.8%)	35 (7.6%)	1.09 [0.62, 1.93]	0.77 [0.37, 1.62]
Fever	12 (6.2%)	4 (2.9%)	32 (6.9%)	0.90 [0.47, 1.71]	0.42 [0.15, 1.17]
Neutropenia	22 (11.4%)	9 (6.6%)	11 (2.4%)	4.79 [2.37, 9.68]	2.76 [1.17, 6.52]
Cutaneous dryness	5 (2.6%)	0 (0.0%)	33 (7.1%)	0.36 [0.14, 0.92]	-
Anemia	11 (5.7%)	4 (2.9%)	26 (5.6%)	1.01 [0.51, 2.01]	0.52 [0.18, 1.46]
TCD Transcranial doppler	18 (9.3%)	17 (12.4%)	2 (0.4%)	21.54 [5.05, 91.95]	28.66 [6.71, 122.5]
Other Not SCD-related events	9 (4.7%)	12 (8.8%)	14 (3.0%)	1.54 [0.68, 3.50]	2.89 [1.37, 6.10]

Source: Siklos® ISS, 5.3.5.3, Table 37

Effect of Age on Risk of Infection
Younger children with sickle cell disease have a greater risk of infection than older children and adults. This finding was supported by the data from ESCORT-HU (as seen in the Table above), and is unlikely to be related to the use of Siklos®, but rather due to the underlying sickle cell disease.

Effect of Age on Risk of Myelosuppression with Siklos® use
Data from ESCORT-HU suggests that children (both 2-10 and 10-16 age groups) had a slightly increased incidence of neutropenia than adults. This may be in part due to the more frequent dose adjustments for weight that occur in children, as well as the overall increase incidence of infection in pediatric patients when compared to adults. Children taking Siklos® should be monitored for myelosuppression at regular intervals, as well as at the time of dose alterations.

There were no interactions between drug safety and patient gender.

7.5.4 Drug-Disease Interactions

No relevant evaluation was completed.

7.5.5 Drug-Drug Interactions

Refer to the Clinical Pharmacology Review

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Pre-clinical data suggests that hydroxyurea may be genotoxic. However, this finding has not been confirmed in humans. As of the data cutoff for this application (February 5, 2016), no secondary cancers have been reported in any pediatric subjects enrolled on ESCORT-HU with a mean exposure of 20.7 ± 18.6 months. A total of 43% of pediatric patients were exposed to hydroxyurea prior to their enrollment on ESCORT-HU, for a mean duration of 4.43 ± 2.88 years (Range, 0.1 to 14.8 years).

The risk for the development of secondary cancers cannot be ruled out and is therefore included in the proposed labeling for Siklos®, including warnings to advise protection from sun exposure and monitor for the development of secondary malignancies.

7.6.2 Human Reproduction and Pregnancy Data

Based on the Siklos® post-marketing safety data in the EU, there have been 19 reported pregnancies in patients taking Siklos®. Of these, 16 were enrolled on ESCORT-HU, and

three pregnancies were in women whose male partner was taking Siklos®. The table below depicts the outcomes of women exposed to Siklos® during pregnancy.

Table 43. Pregancy Outcomes for Women Exposed to Siklos® During Pregnancy

Source	Outcome of pregnancies	Number of cases
ESCORT-HU	Normal birth	5
	Early termination (voluntary or therapeutic)	4
	Premature birth	4
	Ongoing documentation	3
PMS report	Unknown	4

Abbreviation: PMS= Post-marketing safety

Source: Siklos® SS, Table 61

Based on the available data, the risk that exposure of pregnant women to Siklos® may result in birth defects cannot be excluded. Evaluation of the risk-benefit ratio should be made on an individual basis for women of childbearing potential. Women of childbearing potential receiving Siklos® should be advised to use contraception to avoid becoming pregnant. Contraception is recommended for at least 3 months after ending therapy in both women of childbearing potential and males treated with Siklos®. Due to the potential teratogenic effects in animal models, hydroxyurea use is not recommended during pregnancy.

Male Fertility Impairment

Hydroxyurea-induced inhibition of DNA replication in subjects with sickle cell disease may impair the function of the testes and epididymis that rely on DNA transcription. Hydroxyurea may affect the chromatin structure of germ cells mainly in preleptotene spermatocytes and increase apoptosis, essentially in spermatogonia and early spermatocytes.

In animal studies, hydroxyurea has been shown to cause testicular atrophy, decreased spermatogenesis, and reversible decrease in sperm count and motility.

Hydroxyurea has been reported to impair male fertility in humans. Oligospermia and azoospermia have been reported in both adult and pediatric patients with SCD. Because of this potential risk, both oligospermia and azoospermia should be listed in the Adverse Reactions section of the label.

7.6.3 Pediatrics and Assessment of Effects on Growth

Sickle cell disease is associated with impaired growth and overall growth delay. At baseline, growth delay was reported in 33 (8.4%) of pediatric patients enrolled on ESCORT-HU. An overview of the number of patients with growth delay in the Global Safety Set and the Safety Set is provided in the Table below.

Table 44. Baseline Growth Delay in Pediatric Patients Enrolled On ESCORT-HU

Pediatric patients <18 years old	Global Safety Set N=405	Safety Set N=233
Growth delay		
n	392	222
No	359 (91.6%)	207 (93.2%)
Yes	33 (8.4%)	15 (6.8%)
Missing	13	11

Source: Siklos® ISS, Table 28

In ESCORT-HU, one subject, a 7 year-old male, experienced growth retardation categorized as severe while receiving Siklos®.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

In Study ESCORT-HU, one subject in the Global Safety Set, a 12-year-old male, experienced an accidental overdose. He was initially prescribed Siklos® 21 mg/kg/day. Approximately 1 year after treatment initiation, he received 40 mg/kg/day for 3 days due to his caregiver's misunderstanding of his dose. He subsequently developed epistaxis (no laboratory data was provided), which fully resolved. He experienced no additional adverse events.

In the Siklos® post-marketing safety data, ten overdoses have been reported, of which four occurred in pediatric patients.

- 2 cases of medication errors secondary to caregiver's misunderstanding of dosage led to overdoses in 2 children (1 experienced epistaxis, 1 experienced pancytopenia)
- 2 cases in 2 children where overdose occurred after the pharmacy mistakenly dispensed the 1000mg tablets instead of 100 mg tablets (both experienced pancytopenia)

Drug Abuse Potential

There is no evidence of any dependence potential with hydroxyurea use.

Withdrawal and Rebound
No formal studies of rebound or withdrawal have been conducted with hydroxyurea. No particular events have been reported in the pediatric cohort studies in the few patients who had a transient or definite withdrawal of hydroxyurea therapy.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

As indicated above, the review of the Siklos® NDA was based primarily on review of data from ESCORT-HU study, which is an EU post-marketing registry study.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling negotiations are ongoing.

9.3 Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee.

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/s/

RACHEL E ERSHLER
01/11/2017

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Cross Discipline Team Leader Memo

FDA CDER Office of Hematology and Oncology Products
Division of Hematology Products

NDA/BLA #	208843
Product	Siklos
Date	September 27, 2016
CDTL	Nicole Gormley, MD

Background:

The clinical pharmacology team has reviewed the information submitted in BLA 208843 and identified that the bioanalytical raw data for Study OTL-001-1 was not included in the submission. An information request was sent to the sponsor requesting this information, but the sponsor responded that they did not store the raw data because the study was conducted 11 years ago. The clinical pharmacology team has decided that from their standpoint, the omission of this data meets the criteria for a refusal to file.

An internal meeting was held on September 13, 2016 with the clinical, clinical pharmacology, CMC, and biopharmaceutics teams to discuss this issue. The biopharmaceutics team requested that the sponsor submit a (b) (4) request was received by the Agency on September 26, 2016. The Division of Biopharmaceutics has determined that this application should be filed from their standpoint.

While the bioanalytical raw data for Study OTL-001-1 is not available to support bioequivalence, the sponsor has submitted a request (b) (4), and there may not be a need to rely upon the in vivo bioanalytical data from Study OTL-001-1 to support bioequivalence. Ultimately, this will be a review issue.

Decision:

The application for NDA 208843 should be filed.

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/s/

NICOLE J GORMLEY
09/27/2016