STUDY PROTOCOL

Multicentre randomized double-blind placebo-controlled study to evaluate the effect on albuminuria of 6 months treatment with hydroxycarbamide (Siklos®) or a placebo in adults with sickle cell disease: SIKAMIC (SIklos on Kidney function and AlbuMInuria Clinical trial)

Protocol number	SIK-FR-17-1
EUDRACT number	2018-002899-41
Protocol date	22 December 2022
Protocol version	Protocol Amendment 7 Version 1.0
Investigational product name	Siklos® (hydroxycarbamide) 100 mg or 1000 mg film-coated tablets
Indication	Sickle Cell Disease
Sponsor	ADDMEDICA S.A.S. 16 rue Montrosier 92200 Neuilly-sur-Seine, France Tel.: +33 (0)1 72 69 01 86 http://www.addmedica.com *Sponsor Signatory* Laura THOMAS-BOURGNEUF, Clinical Operations Manager
Coordinating Investigator	Professor Pablo BARTOLUCCI Centre de Référence des Syndromes Drépanocytaires Majeurs, Hôpital Henri-Mondor, APHP, Université Paris-Est Créteil 51, avenue du M[al]-de-Lattre-de-Tassigny 94010 Créteil Cedex, France

STUDY ADMINISTRATIVE STRUCTURE

Role/Responsibility	Company/Organisation	Name(s)
Sponsor	ADDMEDICA S.A.S. 16, rue Montrosier 92200 Neuilly-sur-Seine, France Tel.: +33 (0) 172 690 186 http://www.addmedica.com	
Sponsor Signatory	ADDMEDICA S.A.S. 16, rue Montrosier 92200 Neuilly-sur-Seine, France Tel.: +33 (0) 172 690 186 http://www.addmedica.com	Laura THOMAS-BOURGNEUF Tel.: +33 (0) 172 690 186 Fax.: +33 (0) 173 729 413 laura.thomas-bourgneuf@addmedica.com
Project Management & Monitoring	ICTA PM 11 rue du Bocage 21121 FONTAINE LES DIJON FRANCE Tel : +33 (0) 380 534 000 www.icta.fr	Marion DAVID Tel : +33 (0) 380 534 000 marion.david@icta.fr
IMP labelling and packaging	Creapharm Allée des Landais CS10034 51726 Reims Cedex - France Mobile : +33 (0) 620 569 360	
Pharmacovigilance	ADDMEDICA pv@addmedica.com 16, rue Montrosier 92200 Neuilly-sur-Seine, France Tel: +33 (0) 172 690 186 http://www.addmedica.com	
Data Management	ICTA PM 11 rue du Bocage 21121 Fontaine les Dijon, France Tel: +33 (0) 380 534 000 http://www.icta.fr/	Marie-Céline TRIPONNEY Tel : +33 (0) 380 534 000 marie-celine.triponneyt@icta.fr
Biostatistics	ICTA PM 11 rue du Bocage 21121 Fontaine les Dijon, France Tel: +33 (0) 380 534 000 http://www.icta.fr/	Edwige YON Tel : +33 (0) 380 534 000 edwige.yon@icta.fr
Medical Writing	ICTA PM 11 rue du Bocage 21121 Fontaine les Dijon, France Tel: +33 (0)3 80 53 40 00 http://www.icta.fr/	Maria GACKIERE KATSOGIANNOU Tel : +33 (0) 380 534 070 Maria.GACKIERE@icta.fr

Academic Scientific Expert	Professor Vincent Audard Centre de Référence Syndrome Néphrotique Idiopathique Hôpital Henri-Mondor, APHP, Université Paris-Est Créteil 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil
Independent Data Monitoring Committee	• Ms Claire RIGOTHIER, MD, nephrologist, RPPS number : 10004628623, groupe hospitalier Pellegrin place Amelie Raba Leon 33076 Bordeaux cedex, France • Mr Jean-Philippe HAYMANN, MD, nephrologist, RPPS number 10000562909, HU Est parisien site Tenon, AP-HP, service d'explorations fonctionnelles, 4 rue de la Chine, 75970 paris cedex 20, France • Ms Françoise DRISS, MD, RPPS number 10000222819, Hôpital Bicêtre, service d'hématologie, 78, rue du Général Leclerc, 94275 Le Kremlin-Bicêtre Cedex, France • Mr Eric GUEMAS, biostatistician co-founder & CEO at Biossec, 9-11 rue Anatole de la Forge, 75017 Paris, France

PROTOCOL SPONSOR SIGNATURE PAGE

Multicentre randomized double-blind placebo-controlled study to evaluate the effect on albuminuria of 6 months treatment with hydroxycarbamide (Siklos®) or a placebo in adults with sickle cell disease : SIKAMIC (SIklos on Kidney function and AlbuMInuria Clinical trial)

Protocol number	SIK-FR-17-1
EUDRACT number	2018-002899-41
Protocol date	22 December 2022

Sponsor

ADDMEDICA S.A.S.

16, rue Montrosier
92200 Neuilly-sur-Seine, France

Sponsor signatory

Laura THOMAS-BOURGNEUF, Clinical Operations Manager

Date **Signature**

PROTOCOL COORDINATING INVESTIGATOR AND PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Multicentre randomized double-blind placebo-controlled study to evaluate the effect on albuminuria of 6 months treatment with hydroxycarbamide (Siklos®) or a placebo in adults with sickle cell disease : SIKAMIC (SIklos on Kidney function and AlbuMInuria Clinical trial)

Protocol Number	SIK-FR-17-1
EUDRACT Number	2018-002899-41
Protocol Date	22 December 2022

I certify that I will conduct the study in compliance with the protocol, any amendments, GCP and all applicable regulatory requirements.

Coordinating Investigator

Name: Professor Pablo BARTOLUCCI

Institution: Centre de Référence des Syndromes Drépanocytaires Majeurs,
Hôpital Henri-Mondor, APHP, Université Paris-Est Créteil
51, avenue du M[al]-de-Lattre-de-Tassigny
94010 Créteil Cedex, France

Date **Signature**

Principal Investigator

Name:

Date **Signature**

SYNOPSIS

Study rationale:	Sickle cell disease (SCD) is associated with a high frequency of chronic kidney disease (CKD), which constitutes an independent risk factor for death in this population. In term of epidemiology SCD-associated nephropathy (SCAN) is a growing matter of concern because chronic renal failure affects from 12% to 16% of adult patients [1-3]. In elderly patients, renal failure is a major contributor to death [4, 5]. Thus, the early diagnosis of SCAN together with the recognition of the associated clinical and biologic risk factors are of major interest to make it possible to initiate kidney-protective therapy at early stages of renal impairment. SCAN is a progressive condition that begins during childhood. Acidic, hypertonic and hypoxic intrinsic environment of the renal medulla enables HbS polymerisation and erythrocyte sickling within the vasa recta – the capillary networks that supply blood to the medulla. Erythrocytes sickling leads to occlusion of the blood vessels with impairment of blood flow, ischaemia, and infarction of the tubular cells. The ischaemic damage results, in turn, in release of vasodilating substances such as prostaglandins and nitric oxide, which feed back to the glomerulus and tend to increase the glomerular filtration rate. Albuminuria is considered to be a relevant biomarker for the detection of early glomerular damage in patients with sickle cell disease (SCD). A broad spectrum of glomerular diseases has been described in SCD patients, with elevated albuminuria, isolated glomerular enlargement and focal segmental glomerulosclerosis (FSGS) being the most frequent lesions [6]. As observed in diabetic nephropathy, prolonged hyperfiltration firstly observed in SCD probably contribute to progressive renal damage and development of proteinuria. Hyperfiltration and proteinuria are two major causes of subsequent glomerulosclerosis and reduction in kidney function [6-8]. In this first trial we suggest to evaluate the effect of hydroxycarbamide (Siklos®) on albuminuria. <u>Rational for controlled trial versus placebo</u> As yet, there is no definitively proven treatment that slows the progression of glomerular damage in SCD patients. Few therapeutic options are available for the treatment of SCAN. Some authors recommend the use of usual renal protective measures, including renin–angiotensin-system inhibitors (RAS inhibitors) (angiotensin-converting enzyme (ACE) inhibitor and angiotensin II-receptor blocker (ARB)) to reduce the degree of proteinuria and to slow the decline in renal function, although there are no published guidelines in this population on when to introduce this form of therapy [9, 10] . Regardless of underlying renal disease, proteinuria has been known for many years to be associated with rapid progression of chronic kidney disease, and reducing this proteinuria with RAS inhibitors is a key factor to delay glomerular filtration rate (GFR) deterioration in patients with either diabetic or non-diabetic proteinuric renal disease [11]. Several studies in SCD patients have reported possible clinical benefit of these drugs on renal function but generally with small series and short follow-up time. Falk et al (1992) [1] first showed in 10 SCD patients that 2 weeks of enalapril led to a 57% decrease in proteinuria that rebounded after treatment discontinuation. Other authors also found that proteinuria was reduced by 43.3–76.3% in 5 out of 7 SCD patients treated with fosinopril (10 mg daily) for 6 months [12]. These results

	are supported by a 6-month placebo-controlled study on 22 SCD patients, which indicated that captopril significantly reduces microalbuminuria and diastolic blood pressure [13]. A recent phase 2 open label study including 32 participants found that administration of an angiotensin-II-receptor-1 blocker during 6 months significantly decreased albuminuria (albumin-to-creatinine ratio) level [14]. In a prospective multicentric non-randomized trial including 42 SCD patients, Haymann et al showed that ACE inhibitors appears safe and effective in decreasing albuminuria [15]. Nevertheless, to date, no randomized, prospective clinical trials with adequate sample size have clearly demonstrated the potential benefit of RAS inhibitors, and their tolerance among SCD patients. Hydroxycarbamide is one of the cornerstone treatments for the management of SCD patients and its efficacy is generally attributed to its ability to boost the levels of fetal Hb (HbF) [16]. Hydroxycarbamide is known to decrease the frequency of acute pain episodes and acute chest syndrome (ACS), the need for red blood cell transfusions, and the number of hospitalisations. Siklos® is approved since 2007 in the European Union (EU) for the prevention of recurrent painful VOC, including acute ACS, in adult, adolescent and children older than 2 years old suffering from SCD and since 2017 in the United States of America (USA) to reduce the frequency of painful crises and 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. Several observational studies conducted in adult SCD patients have shown that hydroxycarbamide has possible protective renal effects and may be considered as a promising therapeutic option [17, 18]. <u>Rational for the choice of endpoints:</u> Proteinuria begins as microalbuminuria, and progresses to overt macroalbuminuria and nephrotic syndrome, which reflects the worsening of glomerular damage. Microalbuminuria is most often the first clinical indicator of glomerular damage in SCD [8]. According to KDIGO (Kidney Disease: Improving Global Outcomes) Guideline 2013, microalbuminuria also known as moderately increased albuminuria refers to a situation where urine albumin-to-creatinine ratio (ACR) ranges from 3−30 mg/mmol [19]. Macroalbuminuria also known as severely increased albuminuria refers to a situation where ACR ranges from 30 to 300 mg/mmol. The GFR is usually reported as primary endpoint in renal disease however due to the changes of GFR at the beginning of the renal impairment with hyperfiltration, the ACR ratio will be more accurate as primary endpoint. In this study, eGFR will be analysed as a secondary endpoint. Arlet et al (2012) showed that glomerular hyperfiltration, is a frequent finding observed, which is frequently associated with microalbuminuria or macroalbuminuria [20]. In the study of Arlet et al in non-Afro-American SCD patients, the best method for estimating eGFR from serum creatinine seems to be the CKD-EPI equation without adjustment for ethnicity. This equation is particularly accurate to estimate high GFR values, including glomerular hyperfiltration, and thus should be recommended to screen SCD adult patients at high risk for SCD nephropathy.

	<u>Choice of targeted population</u> Renal impairment is common to any clinical phenotypes of SCD however, hemolytic phenotype seems more exposed [21]. Because severe patients with vaso-occlusive phenotype have less renal injuries and are already treated with hydroxycarbamide (HC), they will be excluded from the study. Clinical guidelines recommend the prescription of renin angiotensin system inhibitors (RAS inhibitors) (either ACE inhibitors or angiotensin receptor blockers [ARBs]) only in case of macroalbuminuria with ACR ≥ 100 mg/mmol. Hence patients with ACR ≥ 100 mg/mmol will be excluded from the study. Variations in GFR in SCD at early stages of kidney injury are not fully understood, although the occurrence of hyperfiltration with an increased GFR and concomitant microalbuminuria is likely the first sign of renal impairment. A recent study presented at the last American Society of Hematology meeting by Biemond et al. demonstrated a clear correlation between the long-term subclinical renal function deterioration and microalbuminuria in 167 SC patients [22]. However, as clinical relevance of a decrease in GFR in hyperfiltrating patients is not ascertained in the current state of knowledge, patients with renal hyperfiltration will not be included in the study. <u>Rational for the duration of study</u> A retrospective study of Bartolucci *et al.* suggested that HU administered for 6 consecutive months without concomitant use of RAS inhibitors could significantly decrease urine albumin/creatinine ratio (ACR) [17]. This timepoint has been chosen in the SIKAMIC trial to assess the efficacy of hydroxycarbamide (Siklos®) in achieving at least a 30% decrease of ACR. Only patients qualified as responders after 6 months of treatment will be offered to continue to receive the study treatment and their follow-up will be extended to 6 additional months. The purpose of this phase IIb, international (France and Africa), multicentre, double-blind, randomised, placebo-controlled study is to determine the effect of hydroxycarbamide on albuminuria after 6 months of treatment in SCD adult patients. A 6 months study will allow to better document the natural history of the SCAN and to assess the response to Siklos® in this population.
Objectives:	**Primary objective** The primary objective of this trial is to demonstrate the effect of 6-month treatment with hydroxycarbamide (Siklos®) against placebo in achieving at least a 30% decrease of the albuminuria (albumin to creatinine ratio; ACR) baseline value in adult sickle cell patients. **Secondary objectives** • To compare the estimated GFR (eGFR) according to CKD-EPI formula* between hydroxycarbamide (Siklos®) and placebo group at 6 months. • To compare the proportion of patients in hydroxycarbamide versus placebo group with an improvement in the albmuminuria stage, i.e. a shift from grade A3 to grade A2 albuminuria (macro- to microalbuminuria), from grade A2 to grade A1 albuminuria (micro- to normoalbuminuria) or from grade A3 to grade A1 albuminuria (macro- to

	normoalbuminuria), according to the KDIGO staging system at 6 months. • To compare the proportion of patients in hydroxycarbamide versus placebo group with a renal disease progression supported by an increase in albuminuria at 6 months, as compared to baseline. • To identify some clinical and biological markers potentially associated with response to treatment. • To describe the evolution of ACR from inclusion to month 6. • To describe the evolution of eGFR from inclusion to month 6. • To describe the evolution of ACR of responder patients from inclusion to month 12. • To describe the evolution of eGFR of responder patients from inclusion to month 12. • To evaluate the safety of hydroxycarbamide throughout the entire study period. • To evaluate the impact of the study treatment on SCD-related events throughout the entire study period. **Optional exploratory objective** • To identify any biomarker predictive of SCN (BIOBANK). *eGFR (millilitres per minute per 1.73 m^2) = 141 × min (Scr/k,1)$^{\alpha}$ × max(Scr/k,1)$^{-1.209}$ × 0.993^{Age} × 1.018 (for women), where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.
Study design/assessments:	**Study design:** Phase-IIb, prospective, two-armed, parallel-design, international, multicentric, randomized, double blind, placebo-controlled trial in adult patients with HbSS or HbSβ^0 SCD and ACR between 3 to 100 mg/mmol. The patients will be recruited in France and in Africa. After having given written informed consent (ICF), they will be examined to determine their eligibility according to inclusion/exclusion criteria. The eligible patients will be randomised to receive in a 1:1 ratio: • Hydroxycarbamide (Siklos®) (hydroxycarbamide group) • Placebo (placebo group) Randomization will be stratified according to ACR baseline value: •]3-30 mg/mmol] microalbuminuria • or]30-100 mg/mmol[macroalbuminuria. Treatment will be administered for 6 consecutive months. Patients qualified as 'responders' after 6 months of treatment will be offered to continue the study treatment and their follow-up will be extended to 6 additional months. **Study assessments:** Study assessments will be performed from screening to end-of-study visit (V4 – Month 6 for non-responders, V6 -Month 12 for responders willing to continue the study) or early termination visit in case of deterioration of renal function. Patients will attend a total of 4 to 6 visits at the clinic centre. An overview of the study visits and procedures is presented hereafter and in the flowchart. *Assessment of renal function:* • For ACR calculation, urine albumin and urine creatinine will be assessed on first-morning urine samples collected on 3 consecutive

	days at V2 (inclusion) and V4 (Month 6). This assessment will also be performed at V6 (Month 12), for patients qualified as 'responders' willing to continue the study. Patients will receive a prescription for urine analysis at V1 (screening), V3 and V5 (for responder patients willing to continue). They will be asked to collect at home first morning urine samples (between 6.30 and 8.30 a.m.) in polyethylene containers on 3 consecutive days. Urine samples will be stored at room temperature and the patient will be asked to bring the sample to a local lab of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient • Intermediate analysis of urine albumin and urine creatinine to evaluate ACR will be assessed on one first-morning urine sample at V3 (Month 3) and at V5 (Month 9, for responder patients willing to continue) in order to identify an effect before 6 months of the treatment and to check the sustainability of the effect after 6 months for responder patients (dynamics of the response). • eGFR will be assessed at V1 (screening), V3 (Month 3) and V4 (Month 6). Additional eGFR measurements will be performed atV5 (Month 9) and V6 (Month 12) for patients qualified as 'responders' willing to continue the study. The CKD-EPI method of calculation will be used. eGFR calculation will be automated in the eCRF, based on serum creatinine level, age and sex. *Assessment of vital signs and adverse events:* • Physical examination and blood pressure measurements will be performed at each visit. • SCD-related adverse events will be recorded at each visit. *Assessment of haematological and biochemical parameters:* • Blood samples for haematology will be collected at V1 (screening), Month 1, V3 (Month 3) and V4 (Month 6). Additional blood samples will be collected at V5 (Month 9) and V6 (Month 12) for patients qualified as 'responders' willing to continue the study. Blood samples for creatinine, and haemolysis markers will be collected at V1 (screening), V3 (Month 3) and V4 (Month 6). Additional blood samples will be collected at V5 (Month 9) and V6 (Month 12) for patients qualified as 'responders' willing to continue the study.

FLOW CHART OF STUDY VISITS AND ASSESSMENTS

	Pre-treatment phase		**Treatment phase**				
	Screening	**Inclusion (Randomisation)**	**Follow-up visit**	**Follow-up or End of study visit[1]**	**Follow-up Visit[2]**	**Follow-up Visit[2] End of study/**	**Early termination**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	
Schedule (month/day)	**D-30 - D0**	**D0**	**M3 D90±14**	**M6 D182±14**	**M9 D273±14**	**M12 D365±14**	
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Randomisation		X					
Demographic information	X						
Medical and surgical history	X						
Previous medication(s)[3]	X						
Concomitant medication(s) (CM)	X	X	X	X	X	X	X
Physical examination and blood pressure	X	X	X	X	X	X	X
Semen cryopreservation[4]	X						
Haematology[5]							
Blood sampling	X		X	X	X	X	X
Results		X	X	X	X	X	X
Prescription[6]		X					
Biobank blood sample[7]	X			X		X	X
Biochemistry[8]							
Blood sampling	X		X	X	X	X	X
Results		X	X	X	X	X	X
Screening for HIV, HBV, HCV							
Blood sampling	X						
Results		X					
Pregnancy test[9] for women							
Blood sampling	X						
Result		X					
Check of contraceptive use	X	X	X	X	X	X	X
Urine analysis :							
prescription and a collection kit for urine analysis	X[10]		X[10]		X[10]		
ECBU and Hematuria during 3 consecutive days	X[10]			X[10]		X[10]	X[10]
Urine albumine and urine creatinine for ACR during 3 consecutive days	X[10]			X[10]		X[10]	X[10]
Results		X[11]		X[12]		X[12]	X

Intermediate local analysis of urine albumin and urine creatinine for ACR on one day			X		X		
Biobank blood and urine sample[7]	X			X		X	X
Dispensation of study treatment[13]		X	X	X[14]	X[14]		
Compliance to study treatment			X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X
Diary cards (reporting of drug intake/AE/CM/SCD events)							
- Dispensing		X	X	X	X		
- Collection/review			X	X	X	X	X

ACR: Albumin-to-Creatinine Ratio; AE: Adverse Event; CM: Concomitant Medication; D: Day; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; M: Month; SCD: Sickle Cell Disease; V: Visit.

[1]For unresponsive patients or responsive patients unwilling to continue the study, this visit will be the End of study visit.

[2]Additional visits only for patients qualified as responders and willing to continue the study.

[3]Previous blood transfusions and previous administration of hydroxycarbamide will be reported.

[4]Not required if semen cryopreservation was already performed in the past. If semen volume or viable sperm cell amount is insufficient for cryopreservation of the collected sample, a spermogram will be performed and conserved in CECOS during the whole duration of the study. A control spermogram could be performed in patients at least 6 months and at most 9 months after the last dose of treatment.

[5]The following assessments will be performed: WBC and differential counts, platelets, MCV, MCHC, MCH, Hb, HbF, free Hb, %DRBCs, reticulocytes, endogenous EPO, and ferritin

[6]At V2, prescription will be given for hematology assessment in local lab 1 month after treatment initiation.

[7]Optional exploratory biobank: blood and urine samples for patients from French sites only.

[8]The following assessments will be performed: LDH, AST, ALT, BUN, conjugated and total bilirubin and blood creatinine for glomerular filtration rate (GFR) calculation. The CKD-EPI formula will be used for eGFR calculation. In addition, fasting glycemia and glycated haemoglobin (HbA1c) may be assessed before V2 upon investigator decision.

eGFR (millilitres per minute per 1.73 m^2) = $141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (for women), where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1. eGRF calculation will be automated in the eCRF, based on serum creatinine level, age and sex.

[9]Pregnancy tests will be performed on blood.

[10]At V1 and V3 for all patients, and at V5 for patients qualified as responders and willing to continue the study: patients will receive a prescription and a collection kit for urine analysis. First morning urine samples will be collected between 6. 30 and 8. 30 a.m. during 3 consecutive days before V2 and V4 for all patients, and before V6 for patients qualified as responders willing to continue the study. Assessments of hematuria, CBEU, urine albumin and urine creatinine for ACR evaluation will be performed at a local lab or at investigator's site.

[11]At V2, ACR result will be reported in the CRF and used for randomization.

[12]In case of ACR≥100 mg/mmol, a local assessment of ACR will be performed one month later to confirm ACR result. Patients will receive a prescription and a collection kit for local ACR assessment on first morning urine samples collected during 3 consecutive days.

[13]This study is double-blinded.

[14]Only for patients qualified as responders and willing to continue the study.

Study duration:	Each patient will be enrolled in the study for a duration of 6 months, during which he/she will be taking the placebo or the study treatment (i.e. hydroxycarbamide (Siklos®) on a daily basis). Patients qualified as responders (patient achieving at least a 30% decrease of the ACR

	baseline at 6 months)willing to continue the study will continue the study for 6 additional months (total duration of 12 months) Duration of inclusion period: 49 months Total duration of the study: 61 months Patient withdrawal decision can araise from the patient himself, the investigator or the IDMC. Patients have the right to withdraw their consent at any time and irrespective of the reason. The Investigator has also the right to withdraw patients from the study for the following reasons (including but not limited to): - Patients transfused more than twice during the study, - Patients' inadequate cooperation and compliance with the protocol, - Any life-threatening AE assessed by the Investigator to be related to study procedure or administration of study treatment, - Patients experiencing at least 3 VOC or 1 ACS during the study, - Patients with an increase in ACR requiring, upon investigator's judgement, a treatment with ACE or ARA2, - Development of an intercurrent illness requiring hospitalisation or surgery, - Loss to follow-up. The IDMC stopping rules are defined in the IDMC charter.
Investigational product – Siklos (hydroxycarbamide):	**Formulation:** Hydroxycarbamide (Siklos®) will be supplied as 100 mg or 1000 mg film-coated tablets. Excipients are sodium stearyl fumarate, silicified microcrystalline cellulose and basic butylated methacrylate copolymer. **Administration:** The posology will be based on the patient's body weight (bw). Hydroxycarbamide (Siklos®) will be prescribed at a dose of 15 mg/kg bw/day. The tablet(s) will be taken orally once daily, preferably in the morning before breakfast. In case of toxicity at 15 mg/kg bw/day, hydroxycarbamide (Siklos®) will be temporarily interrupted and/or decreased to 12.5 mg/kg bw/day or 10 mg/kg bw/day before excluding the patient for safety issue. **Storage:** below 30°C.
Reference product (placebo):	**Formulation:** Placebo tablets (each containing sodium stearyl fumarate, sodium starch glycolate (type A), silicified microcrystalline cellulose and basic butylated methacrylate copolymer) will be formulated to be identical in appearance to Siklos®. **Administration:** The tablet will be taken orally once daily, preferably in the morning before breakfast. In case of toxicity at 15 mg/kg bw/day, placebo will be temporarily interrupted and/or decreased to 12.5 mg/kg bw/day or 10 mg/kg bw/day before excluding the patient for safety issue. **Storage:** below 30°C.
Number of patients:	96 patients (48 patients for each study group) in approximately 30 centres in France (32 patients) and 4 centres in Africa (64 patients).

Study population:	Adult men and women with HbSS or HbSβ^0 SCD and a value of albuminuria ACR over 3 mg/mmol and inferior to 100 mg/mmol confirmed by 3 positive urine samples taken one day apart.
Main inclusion criteria:	**Inclusion criteria** Patients must meet all the following inclusion criteria to participate in the study: 1. Signed and dated Informed Consent Form (ICF) by a legally competent patient. 2. Patients above 18 years. 3. Patients with HbSS or HbSβ0 SCD. 4. Patients with a value of albuminuria, assessed by ACR, over 3 mg/mmol and inferior to 100 mg/mmol confirmed by 3 positive urine samples taken one day apart. 5. Female patients of childbearing potential or postmenopausal female with last period < 12 months before screening agreeing to use a highly effective form of contraception (oral, injected or implanted hormonal contraception, intrauterine device, diaphragm, condom, abstinence) during the trial and for 3 months after hydroxycarbamide discontinuation. 6. Male patients with partners of childbearing potential agreeing to use a highly effective contraception during the trial and for 3 months after hydroxycarbamide discontinuation. Men with pregnant or lactating women should be advised to use a barrier method of contraception (condom) to prevent the foetus or breastfed infant from exposure to hydroxycarbamide. 7. Patients who are covered by insurance scheme according to local regulatory requierements
Main exclusion criteria:	**Exclusion criteria** 1. Patients who had severe VOC requiring hospitalisation or ACS within the last 4 weeks preceding screening visit. 2. Patients treated with hydroxycarbamide for any reason within the previous 6 months. 3. Patients who have had chronic blood transfusion or transfusion in the last 3 months. 4. Patients with a history of hypertension (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg) treated with antihypertensive agent belonging to pharmacological class of RAS inhibitor. 5. Patients who have symptoms suggestive of urinary tract infection or patients with gross haematuria. 6. Patients with a concomitant primary kidney disease. 7. Patients with any systemic condition that could result in a glomerulopathy not related to SCD (e.g. diabetes mellitus, active hepatitis B or C infections, HIV infection, systemic lupus erythematosus, inflammatory arthropathies). 8. Patient with a stage 3, 4 or 5 chronic kidney disease (eGFR < 60 mL/min per 1.73 m^2).

	9. Patients with eGFR ≥ 140 ml/min/1,73m² due to the lack of information regarding the magnitude, direction and significance of the trends in eGFR evolution that could be expected in this population 10. Patients requiring long-term treatment with drugs potentially nephrotoxic (see non-exhaustive list). 11. Patients requiring ACE inhibitors or ARBs within the 3 months before inclusion regardless of the indication. 12. Patients requiring long-term treatment with non-steroid anti-inflammatory drugs. 13. Patients who have a treatment which can modify the kidney function (see non-exhaustive list) in the last 3 months. 14. Patients known to be infected with HIV. 15. Female patients who are pregnant or lactating. 16. Unreliable patients including non-compliant patients, patients with known alcoholism or drug abuse or with a history of a serious psychiatric disorder as well as patients unwilling to give informed consent or to abide by the requirements of the protocol. 17. Simultaneous participation in other clinical trials on an investigational medicinal product or previous participation within 30 days before inclusion. 18. Persons in detention by judicial or administrative decision. 19. Patients with chronic conditions that upon investigator judgment may lead to a limited life expectancy.
Evaluation criteria:	Primary endpoint - Efficacy • The primary endpoint of this study is the proportion of patients in the hydroxycarbamide and placebo groups achieving at least a 30% decrease in ACR baseline value at 6 months after treatment initiation. Patients who do not achieve a 30% decrease of the ACR baseline value at month 6 will be considered non-responders. Requirement for therapeutic change from HU to ACE or ARB inhibitors will be considered as a failure. Secondary endpoints - Efficacy • The absolute mean change from baseline in eGFR in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. • The absolute mean change from baseline in ACR in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. • The proportion of patients with an improvement in the albmuminuria stage according to the KDIGO staging system: - Proportion of patients with a shift from grade A3 to grade A2 albuminuria (macro- to microalbuminuria) at 6 months

	- Proportion of patients with a shift from grade A2 to grade A1 albuminuria (micro- to normoalbuminuria) at 6 months - Proportion of patients with a shift from grade A3 to grade A1 albuminuria (macro- to normoalbuminuria) at 6 months. • The proportion of patients progressing from microalbuminuria to macroalbuminuria in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. • Evolution curve of ACR of the hydroxycarbamide and placebo groups from treatment initiation to month 6. • Evolution curve of eGFR of the hydroxycarbamide and placebo groups from treatment initiation to month 6. • Evolution curve of ACR of responder patients willing to continue the study after 6 months, from treatment initiation to month 12. • Evolution curve of eGFR of responder patients willing to continue the study after 6 months, from treatment initiation to month 12. • The identification of clinical and biological markers associated with response to treatment. Secondary endpoints – Safety • The incidence of treatment-emergent AEs and SAEs at each timepoint. • The baseline values and the absolute mean changes from baseline in clinical parameters (BMI, diastolic and systolic blood pressure, heart rate) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation.This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6. • The baseline values and the absolute mean changes from baseline in haematological parameters (WBC, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, endogenous EPO, and ferritin) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6. • The baseline values and the absolute mean changes from baseline in haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin, reticulocytes) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12

	months for responder patients willing to continue the study after month 6. • The rate of SCD-related clinical events (such as VOC including ACS requiring hospitalisation for at least 48 hours, number and duration [days] of hospitalisations, absence of blood transfusions and any sickle cell complications (priapism, cholelithiasis, retinopathy…)) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6. Optional exploratory endpoint • Biomarkers predictive of SCN may be identified (BIOBANK) only for patients included in French sites.
Statistical methods:	**Sample size:** According to the primary endpoint, a responder is defined as a patient achieving at least a 30% decrease of the ACR baseline at 6 months. Assuming a 1:1 treatment allocation ratio, the sample size of 86 evaluable patients will achieve 80% power to detect an absolute difference of 25% in responder rates (35% in the Hydroxycarbamide group and 10% in the Placebo group) using a Chi-2 test with the normal approximation method. The 2-sided significance level is set at 5%. Assuming that around 10% of randomised patients will not be evaluable for the primary outcome measures, 96 patients (48 in each group) should be randomised in this study. **Analysis populations:** The modified Intent-To-Treat (mITT) population, defined as all randomised patients who received at least one dose of the study medication and at least one ACR assessment post-baseline of the primary efficacy measure will be used for the primary efficacy analyses. The Per-Protocol (PP) efficacy population, defined as all patients from the mITT population without any major protocol deviation, will be used for sensitivity efficacy analyses. The safety (SAF) population, defined as all patients who received at least one dose of the study medication, will be used for safety analyses. **Statistical analyses** Eligible patients will be randomised in a 1:1 ratio to either Hydroxycarbamide or Placebo. The randomisation will be stratified by baseline ACR (≤30 mg/mmol and >30 mg/mmol). **Efficacy analysis:** *Primary endpoint*

	The responder rate (ie. percentage of patients achieving at least a 30% decrease of the ACR baseline value at 6 months) will be provided in each group with its 95% confidence interval. Patients requiring a therapeutic change from HC to ACE or ARB inhibitors will be considered as non-responder. Patients with no ACR measure at 6 months will be considered as non-responder. A sensitivity analysis will be done with a Last Observation Carried Forward (LOCF) imputation for patients with no ACR measure at 6 months and without therapeutic change. Both treatment groups will be compared using a Cochran-Mantel-Haenszel method with the stratification variable (ACR baseline ≤30 vs >30 mg/mmol) as adjusted factor. Hypothesis testing will be performed at the two-sided 5% significance level. The 95% confidence interval of the difference between the groups will also be provided. The mITT population will be the main population of analysis for this criterion. *Secondary endpoints* Each secondary efficacy criterion will be summarised at each time point using descriptive statistics. If the primary endpoint is statistically significant, then the secondary endpoint, absolute mean change from baseline in eGFR, will be tested at the 5% significance level. An Analysis of Covariance (ANCOVA) with treatment group and baseline eGFR as fixed effects will be performed. For patients with missing value, a Multiple Imputation method will be used. Details to implement this approach will be provided in the Statistical Analysis Plan (SAP). All other secondary endpoint testing will be considered as exploratory. **Safety analysis** This analysis will be performed on the SAF population. Only Treatment-Emergent Adverse Events (TEAEs), defined as any AE with an onset date on or after the first dose of study treatment or any ongoing event that worsens after the date of the first dose of study treatment, will be analysed. Other Adverse Events will be listed. The incidence of overall TEAEs, Drug-Related TEAEs, SAEs, Grade 3-4 of TEAEs and TEAEs leading to dose reduction or treatment discontinuation will be provided in each treatment group and overall during the first 6 month-period. Incidence of SCD-related events (i.e VOC, ACS, hospitalisations, blood transfusions) will also be described. TEAEs will be summarized by System Organ Class (SOC) and Preferred Terms (PT), according to treatment groups, and compared using a Chi-2 (or a Fisher Exact test, if the Chi-2 conditions of application are not met) at two-sided 5% significance level. The incidence of overall TEAEs, Drug-Related TEAEs, SAEs, Grade 3-4 of TEAEs, and TEAEs leading to dose reduction or treatment discontinuation will also be provided from month 6 to month 12 in each treatment group and overall for patients qualified as responders willing to continue the study. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for the classification of AEs. This will permit to describe the incidence of above AEs by System Organ Class and Preferred Term.

	Other safety endpoints such as vital signs and laboratory data will be descriptively summarised.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin-converting enzyme
ACR	Albumin-to-creatinine ratio
ACS	Acute chest syndrome
AE	Adverse event
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
bw	bodyweight
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	Concomitant medication
CNIL	Commission Nationale de l'Informatique et des Libertés
CPP	Comité de protection des Personnes
CRA	Clinical Research Associate
CRO	Clinical research organisation
DRBC	Dense Red Blood Cell
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPO	ErythroPOietin
ESCORT-HU	European Sickle Cell Disease Cohort – Hydroxyurea
EU	European Union
GFR	Glomerular Filtration Rate
HbA1c	Glycated hemoglobin
Hb	Haemoglobin
HbF	Foetal haemoglobin
HbSS	Homozygous haemoglobin S
HbSβ^0	Heterozygous haemoglobin S / null alleles
HBV	Hepatitis B virus
HCV	Hepatitis C virus
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethic Committee
ITT	Intention-To-Treat
KDIGO	Kidney Disease: Improving Global Outcomes
LDH	Lactate DeHydrogenase
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PP	Per protocol
PT	Preferred term
RAS	Renin-angiotensin system
SAE	Serious adverse event

SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCD	Sickle Cell Disease
SCN	Sickle cell nephropathy
SOC	System organ class
SmPC	Summary of Product Characteristics
VOC	Vaso-occlusive crisis
WBC	White blood cell

TRADEMARKS

The following trademarks are used in the present report.

Note: In the protocol, the name(s) of the product(s) will be written without the superscript symbol ™ or ®.

Trademark	**Generic name**
Siklos®	Hydroxycarbamide

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Sickle Cell Disease (SCD)

Sicke cell haemoglobinopathies are a group of genetic disorders involving, at least, a mutation in the gene encoding the β-globin chain of the haemoglobin (Hb) molecule (βS globin). The subsequent substitution of valine for glutamic acid at the sixth codon of the β-globin chain of the haemoglobin (Hb) molecule leads to the formation of abnormal Hb tetramer (HbS) [23]. Under deoxygenated states, this abnormal haemoglogin becomes polymerised, which distorts the red blood cells into a 'sickle' shape and alters their ability to carry oxygen throughout the body [24, 25].

When the β^S globin gene is inherited in a homozygous manner (HbSS), it may result in a severe disease, better known as Sickle Cell Anemia (SCA), which is characterised by profound anaemia and multiple organ involvement including cerebrovascular events, retinopathy, cardiovascular diseases, and renal damage. SCD affects millions of persons worldwide and in Europe around 3,000 babies are born homozygous for the defective Hb gene each year [26]. Combination of the β^S allele with a null ($Hb\beta^0$) allele, also known as sickle cell beta-thalassemia, results in a condition very similar to HbSS-SCD [23, 27].

1.1.2 Hydroxycarbamide in SCD

Hydroxycarbamide is one of the cornerstone treatments for the management of SCD patients. The precise mechanism involved in improvement of SCD symptoms in patients treated with hydroxcarbamide is unclear. Its efficacy in SCD patients is generally attributed to its ability to boost the levels of foetal Hb (HbF) [16]. Hydroxycarbamide is known to decrease the frequency of acute pain episodes and acute chest syndrome (ACS), the need for red blood cell transfusions, and the number of hospitalisations. Hydroxycarbamide also appears to improve patient survival [16, 28-31]. Siklos® is approved since 2007 in the European Union (EU) for the prevention of recurrent painful VOC, including acute ACS, in adult, adolescent and children above 2 years old suffering from symptomatic sickle cell syndromes and since 2017 in the United States of America (USA) to reduce the frequency of painful crises and the need for blood transfusions in pediatric patients aged 2 years and older with sickle cell anemia with recurrent moderate to severe painful crises.

1.1.3 Renal abnormalities in SCD

Over the last 20 years, improved care of patients with SCD has increased life expectancy [32]. With improved survival, more long-term complications have become evident [8, 32]. Sickle cell nephropathy (SCN) is one of the most frequent and severe complications experienced by patients with SCD and becomes a growing matter of concern [10]. It is a progressive condition that begins during childhood and encompasses a large spectrum of renal abnormalities including, but not limited to, urinary concentrating defect, haematuria,

renal papillary necrosis, renal tubular dysfunctions, glomerular disease, acute kidney injury, chronic kidney disease, and renal medullar carcinoma (Table 1) [21, 33]. In studies performed on large cohorts of SCD patients, 12 to 16% of adult patients were diagnosed with renal failure [2, 3]. In elderly patients, renal failure is a major contributor to death [4, 5]. The average age at which a patient develops renal failure is 40 years, but previous works have reported the occurrence of SCN very early in childhood, as soon as 7 years of age [8, 34].

Acidic, hypertonic and hypoxic intrinsic environment of the renal medulla enable HbS polymerisation and erythrocyte sickling within the vasa recta – the capillary networks that supply blood to the medulla. Erythrocytes sickling leads to occlusion of the blood vessels with impairment of blood flow, ischaemia, and infarction of the tubular cells. Repeated sickling causes progressive destruction of the vasa recta which results in turn in a urinary concentrating defect. The ischaemic damage may also stimulate the release of vasodilating substances such as prostaglandins and nitric oxide, which feed back to the glomerulus and tend to increase the glomerular filtration rate (GFR). Prolonged hyperfiltration triggers renal damage and proteinuria which in turn engenders glomerulosclerosis and reduction in kidney function [7, 8, 35, 36].

Table 1 Renal abnormalities in SCD

Renal abnormalities [7, 8, 33, 36]	Causes	Epidemiology	Comments
Urinary concentrating defect	Distal tubular dysfunction due to the destruction of the vasa recta by repeated ischaemia.	Among the most frequent renal abnormalities. In the BABY HUG trial, 20.1% (37/184) children were hyposthenuric [34].	As early as infancy. Progresses with age.
Acidification defect	Distal tubular dysfunction due to impaired medullary perfusion.	Retrospective analyses of over 400 patients with SCD demonstrated that 40% of patients exhibited metabolic acidosis [37].	
Impaired potassium excretion	Distal tubular dysfunction due to impaired medullary perfusion.		Serum K level does not generally increase. However, hyperkalaemia may become apparent with progressive renal insufficiency or following use of ACE inhibitors.
Increased secretion of uric acid and creatinine	Hyperfunction of proximal tubule.		Urate clearance decreases with age and the incidence of hyperuricemia increases as renal function deteriorates.
Increased reabsorption of phosphate and β2-microglobulin	Hyperfunction of proximal tubule.		Associated with hyperphosphatemia.
Haematuria	Vascular occlusion in the renal medulla by sickled erythrocytes. Another cause of haematuria is papillary necrosis. Rarely caused by renal medullary carcinoma.	Among the most frequent renal abnormalities.	Usually painless and self-limited, 80–90% unilateral.

Renal papillary necrosis	Vascular occlusion in the renal medulla by sickled erythrocytes.	Frequent renal abnormalities. Renal papillary necrosis has an incidence of 2.3% in SCD patients [38].	Typically associated with haematuria.
Increased GFR	Release of vasodilating substances during the process of sickling.	Glomerular hyperfiltration has a prevalence of 30–51% in HbSS-SCD patients [39, 40].	GFR rate declines towards normal during adolescence and falls to subnormal levels as patient's age and chronic kidney disease progress.
Glomerular abnormalities and proteinuria	Glomerular hyperfiltration; cytokines; iron overload.	In a recent prospective study involving 300 SCD adult patients, the prevalence of albuminuria was 68%. Microalbuminuria was present in 42% of patients and macroalbuminuria in 26% of patients [41].	Proteinuria begins as microalbuminuria and progresses to overt proteinuria as the kidney sustains further damage resulting from the underlying SCD.
Acute kidney injury	Volume depletion; severe sepsis; rhabdomyolysis.	Present in 4−11% of hospitalised patients with SCD [3, 42].	Haemodynamic stress of pregnancy may precipitate it.
Chronic kidney disease	Progressive parenchymal damage and chronic glomerular disease.	Incidence of 4–18% in adults in USA [5, 43].	

ACE: Angiotensin-converting enzyme GFR: Glomerular filtration rate; SCD: Sickle Cell Disease.

1.1.4 Glomerular abnormalities and albuminuria

Glomerular abnormalities are one of the most prominent features of SCN. It is characterised by an isolated glomerular enlargement and focal segmental glomerulosclerosis (FSGS), and an early increase in the GFR associated with proteinuria [6]. As observed in diabetic nephropathy, prolonged hyperfiltration firstly observed in SCD probably contributes to the progressive renal damage and the development of proteinuria. Hyperfiltration and proteinuria are two major causes of subsequent glomerulosclerosis and reduction in kidney function [6-8]. Proteinuria begins as microalbuminuria. As the kidney sustains further damage resulting from the underlying SCD, microalbuminuria progresses to macroalbuminuria and finally to overt proteinuria [8].

Early detection of SCN is key to start effective therapeutic interventions that would prevent the progression of renal damage, before it becomes irreversible. Microalbuminuria is most often the first clinical indicator of glomerular damage in SCD. Microalbuminuria refers to a urinary albumin concentration that is abnormally high but not high enough to be picked up by a simple dipstick [44, 45]. According to the albuminuria staging system established by KDIGO (Kidney Disease: Improving Global Outcomes), microalbuminuria, also known as moderately increased albuminuria, refers to grade A2 albuminuria where urine albumin-to-creatinine ratio (ACR) ranges from 30−300 mg/g or 3−30 mg/mmol and macroalbuminuria, also known as severely increased albuminuria, to grade A3 albuminuria where ACR is > 300 mg/g or 30 mg/mmol [19].

In a study conducted on 300 adult US patients, microalbuminuria occured in ~42% of patients with HbSS SCD, although its prevalence can vary depending on age and SCD genotype [41]. Consistent with these US data, Haymann et al (2010) reported that the prevalence of microalbuminuria was around 40% among 280 adult French patients with HbSS SCD [40]. Of note, macroalbuminuria was reported in 20% to 40% of patients with HbSS SCD depending on the age, and might lead to nephrotic syndrome, revealing a broad spectrum of glomerular lesions, and ultimately, to renal failure [1, 6, 41].

1.1.5 Management of microalbuminuria/proteinuria in SCD patients:

Few therapeutic options are available for the treatment of SCD patients with proteinuria/microalbuminuria. Table 2 summarises studies reporting effects of various therapeutic interventions on proteinuria/microalbuminuria in SCD patients.

Reducing proteinuria with inhibitors of the renin-angiotensin system (RAS inhibitors) (either angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) is a key factor to delay GFR deterioration in patients with either diabetic or non-diabetic proteinuric renal disease [11]. Several studies in SCD patients have reported possible clinical benefit of these drugs on proteinuria levels but generally with small series and short follow-up time. Falk et al (1992) first showed in 10 SCD patients that 2 weeks of enalapril led to a 57% decrease in proteinuria that rebounded after treatment

discontinuation [1]. Other authors also found that proteinuria was reduced by 43.3 to 76.3% in 5 out of 7 SCD patients treated with fosinopril (10 mg daily) for 6 months [12]. These results are supported by a 6-month placebo-controlled study on 22 SCD patients, which indicated that captopril significantly reduces microalbuminuria and diastolic blood pressure [13]. A recent phase 2 open label study including 32 participants found that administration of an angiotensin-II-receptor-1 blocker during 6 months significantly decreased albuminuria (albumin-to-creatinine ratio) level [14]. In a prospective multicentric non-randomized trial including 42 SCD patients, Haymann et al showed that ACE inhibitors appears safe and effective in decreasing albuminuria [15]. Nevertheless, to date, no randomised, prospective clinical trials with adequate sample size have clearly demonstrated the potential benefit of RAS inhibitors, and their tolerance among SCD patients.

In one retrospective review of 23 children with SCD, Alvarez et al (2006) suggested that chronic transfusions starting at an early age protect against microalbuminuria [46]. Another retrospective review failed to confirm this effect and reported similar microalbuminuria frequency in paediatric patients on chronic transfusions (26%) and in those receiving no treatment (24%) [47]. The potential renoprotective effects of transfusion therapy in SCD patients remain controversial and still need to be firmly established.

1.1.6 Hydroxycarbamide in SCAN management

Several observational studies, especially in the adult population, have provided evidence that hydroxycarbamide would be beneficial in SCD patients with impaired glomerular function and may therefore be considered as a promising therapeutic option in this indication.

In the paediatric population, hydroxycarbamide treatment has been shown to have possible renal protective effects in individual studies, but this has not been consistently reported in the literature [47-49]. In the BABY HUG randomised clinical trial, Alvarez et al (2012) failed to show improvement in GFR in toddlers treated for 2 years with hydroxycarbamide [50]. No significant decrease in microalbuminuria was found in SCD children taking hydroxycarbamide for 3 years in the study recently conducted by Aygun et al (2013) [51]. Since the study was carried out on a limited number of patients, no definite conclusion can be drawn.

In SCD adult patients, no randomised, prospective clinical trial has evaluated the potential benefit of hydroxycarbamide on microalbuminuria in adult SCD patients. A case-control study reported that hydroxycarbamide treatment lessens proteinuria but not microalbuminuria in adult SCD patients, suggesting a possible kidney protection [52]. A cross-sectional study showed lower albuminuria levels and lower microalbuminuria prevalence in patients after ≥ 3 months of treatment with hydroxycarbamide compared to patients not treated with hydroxycarbamide [18]. These results are further supported by a recent cohort study showing significant decrease in urine ACR after 6 months of

hydroxycarbamide treatment (median hydroxycarbamide dose at month 6 was 15 [12–18] mg/kg per day) in 58 SCD adult patients [17].

Table 2 Summary of studies reporting therapeutic interventions in SCD patients with proteinuria/microalbuminuria

Reference	Number of patients	Age	Type of study	Treatment(s)	Outcomes
Falk et al [1]	381	Adult	Prospective	Enalapril	In 10 patients treated with enalapril, mean reduction in proteinuria of 57% from baseline after 2 weeks.
Foucan et al [13]	22	Adult	Randomised prospective	Captopril	Significant decrease in microalbuminuria after 6 months.
Voskaridou et al [12]	7	Adult	Prospective	Fosinopril	In 7 patients treated with fosinopril, 5 reduced the degree of proteinuria by 43.3 to 76.3%.
Alvarez et al [46]	23	Paediatric	Retrospective	Hydroxycarbamide or chronic transfusions	Patients who did not have microalbuminuria started transfusions at a younger age (7.78 ± 3.7 years) compared to those who had microalbuminuria (12.2 ± 1.9 years).
Lebensburger et al [47]	144	Paediatric	Retrospective	Hydroxycarbamide or chronic transfusions	Lower microalbuminuria frequency in hydroxycarbamide-treated patients compared to those not receiving this drug (13% and 24%, respectively). Similar microalbuminuria frequency for patients on chronic transfusions (26%).
Aygun et al [51]	23	Paediatric	Prospective	Hydroxycarbamide	Microalbuminuria did not decrease in children taking hydroxycarbamide for 3 years.
Alvarez et al [50]	193	Paediatric	Randomised prospective	Hydroxycarbamide	No improvement in glomerular filtration rate in young children treated for 2 years with hydroxycarbamide.
Silva Junior et al [52]	26	Adult	Prospective	Hydroxycarbamide	Significant decreases in proteinuria but not in microalbuminuria.

Laurin et al [18]	149	Adult	Cross-sectional	Hydroxycarbamide	Lower albuminuria levels and lower microalbuminuria prevalence in patients after ≥ 3 months of treatment compared to untreated patients.
Bartolucci et al [17]	58	Adult	Prospective	Hydroxycarbamide	Significant decrease in urine albumin-to-creatinine ratio after 6 months of treatment (highest decline in the subgroup of patients with baseline microalbuminuria).

SCD: Sickle Cell Disease.

1.2 RATIONALE FOR THE STUDY

Early recognition of SCN and focus on the early steps of the natural history of this nephropathy, together with the recognition of the associated clinical and biologic risk factors are of major interest to make it possible to initiate kidney-protective therapy at early stages of renal impairment. Microalbuminuria is most often the first clinical indicator of glomerular damage in SCD [53]. A broad spectrum of glomerular diseases has been described in SCD patients, with elevated albuminuria, isolated glomerular enlargement and focal segmental glomerulosclerosis (FSGS) being the most frequent lesions [21, 33]. In this first trial we suggest to evaluate the effect of hydroxycarbamide (Siklos®) on albuminuria.

Siklos® was granted an orphan drug designation in the European Union (EU) in 2003 for the treatment of Sickle Cell Syndrome and in the United States of America (USA) in July 2013 for the treatment of SCD in patients under 18 years of age. Siklos® was authorised for marketing in Europe in June 2007 for the prevention of recurrent painful vaso-occlusive crises (VOC) including ACS in adults, adolescents, and children older than 2 years suffering from symptomatic Sickle Cell Syndrome (see Summary of Product Characteristics [SmPC]) and since 2017 in the USA to reduce the frequency of painful crises and 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.

Siklos® is a proprietary formulation of hydroxycarbamide available in 2 dosages (i.e. a 1000 mg scored film-coated tablet and a 100 mg scored film-coated tablet) that enables flexible dosing in 50, 100 mg and 250 mg intervals to meet the specific needs of SCD patients, specifically young patients.

The purpose of this randomised, prospective clinical trial is to confirm results from previous observational studies and to demonstrate the renal protective effect of Siklos® in adult SCD patients with albuminuria treated over a period of 6 months. It is designed to support an extension of Siklos® approved indication to treatment of SCD patients with renal dysfunction.

1.3 RISK/BENEFIT ASSESSMENT

Siklos® 100 mg or 1000 mg film-coated tablets is a widely accepted medical treatment for patients with SCD. During the study, Siklos® will be used according to the recommended dose regimen in the EU label (15 mg/kg bodyweight [bw]/day) and will be adjusted according to patient response and tolerance to treatment.

Known undesirable effects of Siklos® are documented in the SmPC of Siklos effective at the time of the eventThe most frequently reported adverse reaction is bone marrow depression with neutropenia as the most common manifestation. In the present study, blood counts will be monitored closely throughout treatment with Siklos®. If blood counts are within the toxic range, Siklos® will be temporarily discontinued until blood counts recover.

The Investigator can also decide in patient's health interest to withdraw the patient from the study.

The safety profile of Siklos® is still under evaluation. Upon request of the European Medicines Agency (EMA), the ESCORT-HU (European Sickle Cell Disease Cohort – Hydroxyurea) study has been implemented in some countries in Europe for the collection of information about long-term safety of Siklos®. Investigators and patients participating in the SIKAMIC study will be promptly informed about any new safety signal revealed by the ESCORT-HU study.

2. STUDY OBJECTIVES

2.1 PURPOSE OF THE STUDY

The purpose of this phase IIb, international (France and Africa), multicentre, double-blind, randomised, placebo-controlled study is to determine the effect of hydroxycarbamide on albuminuria after 6 months of treatment in SCD adult patients.

2.2 PRIMARY OBJECTIVE

The primary objective of this trial is to demonstrate the effect of 6-month treatment with hydroxycarbamide against placebo in achieving at least a 30% decrease of the albuminuria (albumin to creatinine ratio; ACR) baseline value in adult sickle cell patients.

2.3 SECONDARY OBJECTIVES

The secondary objectives are:

- To compare the estimated GFR (eGFR) according to CKD-EPI formula* between hydroxycarbamide and placebo group in order to evaluate a possible renal protective effect of hydroxycarbamide on eGFR at 6 months.
- To compare the proportion of patients in hydroxycarbamide versus placebo group with an improvement in the albmuminuria stage, *i.e.* a shift from grade A3 to grade A2 albuminuria (macro- to microalbuminuria), from grade A2 to grade A1 albuminuria (micro- to normoalbuminuria) or from grade A3 to grade A1 albuminuria (macro- to normoalbuminuria), according to the KDIGO staging system at 6 months.
- To compare the proportion of patients in hydroxycarbamide and placebo group with a renal disease progression supported by an increase in albuminuria at 6 months, as compared to baseline.
- To identify clinical and biological markers associated with response to treatment.

*eGFR (millilitres per minute per 1.73 m^2) = $141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (for women), where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is -0.329

for women and -0.411 for men, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

- To describe the evolution of ACR from inclusion to month 6.
- To describe the evolution of eGFR from inclusion to month 6.
- To describe the evolution of ACR of responder patients from inclusion to month 12.
- To describe the evolution of eGFR of responder patients from inclusion to month 12.
- To evaluate the safety of hydroxycarbamide throughout the entire study period.
- To evaluate the impact of the study treatment on SCD-related events throughout the entire study period.
- Optional exploratory objective: to identify any biomarker predictive of SCN (BIOBANK).

3. STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

The design of this study is a Phase-IIb, prospective, two-armed, parallel-design, international, multicentric, randomized, double blind placebo-controlled trial in adult patients with HbSS or HbSβ^0 SCD and ACR between 3 and 100 mg/mmol.

The patients will be recruited in approximately 30 centres in France and 4 in Africa. After having given written informed consent (ICF), around 140 patients will be screened to determine their eligibility according to inclusion/exclusion criteria. In fine, around 96 patients (32 patients in France and 64 patients in Africa) will be randomised. At the screening visit (V1), patients will be examined to establish eligibility according to inclusion/exclusion criteria. The screening visit (V1) will take place no more than 30 days prior to the inclusion visit (V2, Day 0) and will allow albuminuria (ACR between 3 and 100 mg/ mmol) to be confirmed by 3 positive urine samples taken one day apart.

At the inclusion visit (V2), the eligible patients will be randomised to receive in a 1:1 ratio:

- Hydroxycarbamide (Siklos®) 15 mg/kg bw/day: hydroxycarbamide group
- Placebo 15 mg/kg bw/day: placebo group

Randomization will be stratified according to ACR baseline value (≤ or >30 mg/mmol). The treatment will be administered for 6 consecutive months. In case of consent withdrawal, unacceptable toxicity or non-compliance to the protocol, the study treatment will be discontinued. Only patients qualified as responders after 6 months of treatment will be offered to continue to receive the study treatment and their follow-up will be extended to 6 additional months.

Patients will attend a total of 4 visits at the clinical centre:

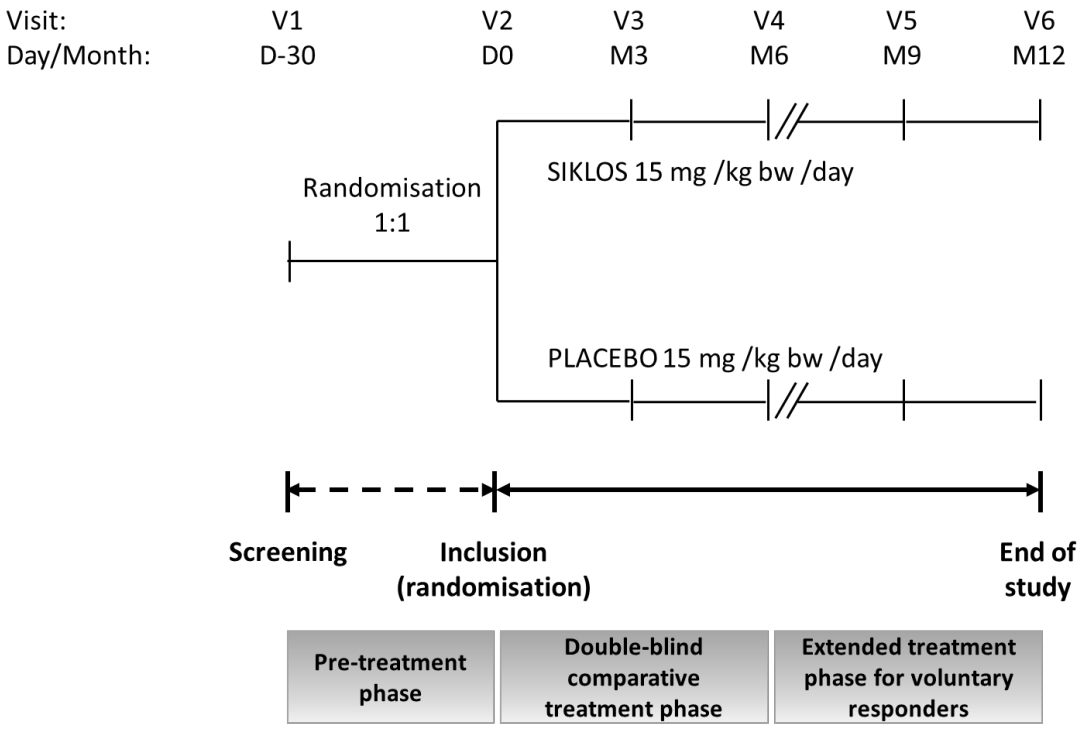
- one screening visit (V1),

- one inclusion/randomisation visit (V2),
- 2 visits during the treatment phase (V3 and V4).

Patients qualified as 'responders' willing to continue the study will continue the treatment and attend two additional visits (V5 and V6) at the clinical centre.

An overview of the study design is provided in Figure 1.

Figure 1 Study scheme



bw: bodyweight; D: Day; M: Month; V: Visit.
V1: screening visit; V2: inclusion visit; V3−V6: follow-up visits

3.2 RATIONALE FOR THE STUDY DESIGN

The study has been designed as randomised and double-blind to allow unbiased study assessments.

No evidence-based treatments are currently available for adult SCD patients with early signs of kidney injury. Although a potential benefit of RAS inhibitor has been observed there is, to date, no clear evidence supporting an association between RAS inhibitors administration and a reduction of albuminuria and proteinuria in patients with SCD (Table 2). Similarly, the renoprotective effects of transfusion therapy remains controversial

and have not been formally confirmed by prospective clinical trials (Table 2). In the absence of a reference treatment, a head-to-head study would not be an adequate strategy; therefore, the study has been designed as placebo-controlled.

3.3 ENDPOINTS

3.3.1 Primary endpoint - Efficacy

The primary endpoint of this study is the proportion of patients in the hydroxycarbamide and placebo groups achieving at least a 30% decrease in ACR baseline value at 6 months after treatment initiation. Patients who do not achieve at least a 30% decrease of the ACR baseline value at month 6 will be considered non-responders.

Rationale for the selection of the primary endpoint:

The GFR is usually reported as primary endpoint in renal disease. However due to the changes of GFR at the beginning of the renal impairment with hyperfiltration, the ACR ratio will be more accurate as primary endpoint.

Albuminuria is increased excretion of urinary albumin and a marker of kidney damage. Persistent increased protein in the urine (two positive tests over 3 or more months) is the principal marker of kidney damage, acting as an early and sensitive marker in many types of kidney disease. A 30% decrease in ACR (so-called 'responders') is commonly used in diabetic studies to determine the efficacy of various therapeutic interventions on albuminuria.

3.3.2 Secondary endpoints - Efficacy

The secondary efficacy endpoints are:

- The absolute mean change from baseline in eGFR in the hydroxycarbamide and placebo groups at 6 months after treatment initiation.
- The absolute mean change from baseline in ACR in the hydroxycarbamide and placebo groups at 6 months after treatment initiation.
- The proportion of patients with an improvement in the albmuminuria stage according to the KDIGO staging system :
    - Proportion of patients with a shift from grade A3 to grade A2 albuminuria (macro- to microalbuminuria) at 6 months
    - Proportion of patients with a shift from grade A2 to grade A1 albuminuria (micro- to normoalbuminuria) at 6 months
    - Proportion of patients with a shift from grade A3 to grade A1 albuminuria (macro- to normoalbuminuria) at 6 months.
- The proportion of patients progressing from microalbuminuria to macroalbuminuria in the hydroxycarbamide and placebo groups at 6months after treatment initiation.
- Evolution curve of ACR of the hydroxycarbamide and placebo groups from treatment initiation to month 6.
- Evolution curve of eGFR of the hydroxycarbamide and placebo groups from treatment initiation to month 6.

- Evolution curve of ACR of responder patients willing to continue the study after 6 months, from treatment initiation to month 12.
- Evolution curve of eGFR of responder patients willing to continue the study after 6 months, from treatment initiation to month 12.
-
- The identification of clinical and biological markers associated with response to treatment.

3.3.3 Secondary endpoints - Safety

The secondary safety endpoints are:

- The incidence of treatment-emergent AEs and SAEs.
- The baseline values and the absolute mean changes from baseline in clinical parameters (BMI, diastolic and systolic blood pressure, heart rate) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6.
- The baseline values and the absolute mean changes from baseline in haematological parameters (WBC, platelets, MCV, MCHC, MCH, Hb, HbF, free Hb*, %DRBCs*, endogenous EPO* and ferritin) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6.
- The baseline values and the absolute mean changes from baseline in haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin, reticulocytes) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6.
- The rate of SCD-related clinical events (such as VOC including ACS requiring hospitalisation for at least 48 hours, number and duration [days] of hospitalisations, absence of blood transfusions and any SC complications: priapism, cholelithiasis, retinopathy….) in the hydroxycarbamide and placebo groups at 6 months after treatment initiation. This analysis will also be performed at 12 months for responder patients willing to continue the study after month 6.

Optional exploratory endpoint : Biomarkers predictive of SCN may be identified (BIOBANK) for patients included in french sites.

* In centres able to do these analyses

3.4 STUDY DURATION

The total duration of the study is expected to be approximately 61 months, after the protocol has been approved by the regulatory authorities and the Independent Ethics

Committee (IEC) and the initiation of the centres. This includes the periods necessary for patient recruitment (49 months) and patient follow-up (12 months).

Each patient will be enrolled in the study for a duration of 6 months, during which he/she will be taking the placebo or the study treatment (i.e. hydroxycarbamide) on a daily basis. The study duration will be extended to 12 months for patients qualified as responders willing to continue to participate in the trial.

3.5 IDENTIFICATION OF PATIENTS

At the screening visit, once a patient has signed the ICF, he/she will be assigned a 6-digit identification number. The first 3 digits will identify the investigational centre (**001**) and the last 3 digits will correspond to the chronological entry order of the patient in the study of that specific centre (001-**099**). The first selected patient in centre 001 will therefore be allocated the patient identification number 001-001. The following patients will subsequently be assigned the identification numbers 001-002, 001-003…The patient will retain this identification number throughout the study (all documents, blood samples…).

If a selected patient becomes ineligible for the study, his/her identification number will not be reallocated to another patient. Individuals who do not meet the criteria for participation in this study (screen failure) may actually be rescreened and rescreened participants will be assigned the same participant number as for the initial screening.

3.6 RANDOMISATION AND BLINDING

3.6.1 Randomisation

A total of approximately 96 patients will be randomly assigned in a 1:1 ratio to either hydroxycarbamide or placebo according to a central computer-generated randomisation scheme. Randomisation numbers will be allocated sequentially according to a central allocation system (IWRS, Interactive Web Response System) to limit selection bias. The randomisation number for each patient will be composed of 3 digits (from 001 to 999) and will be allocated at V2 (inclusion) after verifying the eligibility criteria.

The 24-hour web based randomisation system will be created using the system that is developed and maintained by ICTA.

Randomisation will be stratified according to ACR baseline value (≤ or >30 mg/mmol).

The randomisation list will be prepared by ICTA under the responsibility of the statistician.

3.6.2 Blinding/Unblinding

The study is double-blind, which means neither the patients nor the Investigator or other site personnel or the Sponsor or designee will be aware of the randomisation. Blinding will be maintained by the following measures:

1. The study treatments will be packaged according to a computer-generated randomisation code prepared for all study centres.

2. The randomisation code will not be available to any person involved in the conduct and evaluation of the study until the study database is declared clean and is frozen. Freezing consists in preventing any change in the database. After the randomisation table will be loaded, the database will be locked and released to the statistician.
3. Hydroxycarbamide and placebo tablets will be presented as identical tablets concerning the colour, size, shape, and weight. They will be packed in identical bottles, bearing an identification label.

Unblinding of individual patient treatment

Breaking of blind for an individual patient by the Investigator will only be made if the safety of a patient can no longer be guaranteed and unblinding is an absolute requirement to decide a further treatment of the patient.

Code breaking for any other reason than safety will be considered as 'major violation' and will lead to the exclusion of the patient from the study.

Unblinding will be achieved by the Investigator through the IWRS integrated in the eCRF system and as per the corresponding manual that will be provided to each centre.

An alert via email (sikamic@addmedica.com) will be automatically sent by IWRS in case of request of unblinding by one investigator. If the reason of unblinding is a SAE, the investigator will immediately complete and send by email the "SAE Form" to the sponsor. In any case, the treatment received by the patient and the patient number must not be indicated on the form.

A sponsor's pharmacovigilance representative will also be commited to unblinding decision in case of major safety issue.

Breaking the blind code must remain exceptional and performed only in case of emergency for the patient. In this eventuality, the following information must be recorded in the source document and captured in the eCRF: the date when the randomisation code was broken, the name(s) of the person(s) conducting the code break, and the reason for the code break. The unblinding result should not be reported. Care should be taken to store the unblinding information such that the information is kept confidential.

3.7 WITHDRAWAL AND REPLACEMENT OF PATIENTS

3.7.1 Withdrawal of patients

Patient withdrawal decision can araise from the patient himself, the investigator or the IDMC.

- Patients have the right to withdraw their consent at any time and irrespective of the reason.
- The Investigator has also the right to withdraw patients from the study for the following reasons (including but not limited to):
  - Patients transfused more than twice during the study,
  - Patients' inadequate cooperation and compliance with the protocol,
  - Any life-threatening AE assessed by the Investigator to be related to study procedure or administration of study treatment,
  - Patients experiencing at least 3 VOC or 1 ACS during the study,
  - Patients with an increase in ACR requiring, upon investigator's judgement, a treatment with ACE or ARA2,
  - Development of an intercurrent illness requiring hospitalisation or surgery enforcing a stop of study treatment for more than 15 days,
  - Loss to follow-up.

- IDMC stopping rules defined in IDMC Charter (See Section 3.8).

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Should a patient decide to withdraw, all efforts will be made to collect data as thoroughly as possible. When possible, the patients will be assessed using the procedures planned, the end-of-study visit and the end-of-study form will be completed (see Section 5.4) and the reason for withdrawal should be documented in the eCRF.

Every effort will be made to contact patients who fail to return for a planned visit. If all these attempts to contact the participant fail, the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the source medical file.

Patients who have been withdrawn from the study cannot be re-included in the study. Their identification and randomisation number must not be re-used.

3.7.2 Replacement of patients

Patients with inadequate cooperation and compliance with the protocol may be considered not evaluable and may be replaced, up to the limit of 20% of replaced patients.

3.8 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established prior to study enrolment. All members will be independent from the Sponsor.

The IDMC experts will review cumulative study data every 3 to 6 months to evaluate the safety, study conduct, and scientific validity and integrity of the study. The IDMC will make recommendations regarding the continuation, suspension or termination of the clinical study.

Composition, role and frequency of IDMC meetings are detailed in the IDMC Charter.

3.9 PREMATURE TERMINATION OR SUSPENSION OF THE STUDY

ADDMEDICA S.A.S. reserves the right to temporarily suspend or prematurely terminate this study at any time for reasonable medical or administrative reasons such as failure to enrol patients, suspected lack of efficacy or questionable safety of the study treatment. The sponsor should promptly inform the Investigators/institutions, the IECs and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The Investigators/institutions should also promptly inform the study patients, and should ensure appropriate therapy and follow-up for the patients.

In addition, ADDMEDICA S.A.S. has the right to discontinue a single centre at any time during the study for medical or administrative reasons such as unsatisfactory enrollment, Good Clinical Practice (GCP) noncompliance, inaccurate or incomplete data collection, falsification of records, failure to adhere to the study protocol.

4. STUDY POPULATION

4.1 CHOICE OF TARGETED POPULATION

Renal impairment is common to any clinical phenotypes of SCD however, hemolytic phenotype seems more exposed [21]. Because severe patients with vaso-occlusive phenotype have less renal injuries and are already treated with HU, they will be excluded from the study.

Clinical guidelines recommend the prescription of renin angiotensin system inhibitors (RAS inhibitors) (either ACE inhibitors or angiotensin receptor blockers [ARBs]) only in case of macroalbuminuria with ACR ≥ 100 mg/mmol. Hence patients with ACR ≥ 100 mg/mmol will be excluded from the study.

Variations in GFR in SCD at early stages of kidney injury are not fully understood, although the occurrence of hyperfiltration with an increased GFR and concomitant microalbuminuria is likely the first sign of renal impairment. A recent study presented at the last American

Society of Hematology meeting by Biemond et al. demonstrated a clear correlation between the long-term subclinical renal function deterioration and microalbuminuria in 167 SC patients [22]. However, as clinical relevance of a decrease in GFR in hyperfilttrating patients is not ascertained in the current state of knowledge, patients with renal hyperfiltration will not be included in the study.

4.2 INCLUSION CRITERIA

The inclusion criteria are to be verified at the screening and inclusion visits (V1 and V2). Patients must meet ALL the following inclusion criteria to participate in the study:

1. Signed and dated Informed Consent Form (ICF) by a legally competent patient.
2. Patients above 18 years.
3. Patients with HbSS or HbSβ^0 SCD.
4. Patients with a value of albuminuria, assessed by ACR, over 3 mg/mmol and inferior to 100 mg/mmol confirmed by 3 positive urine samples taken one day apart.
5. Female patients of childbearing or postmenopausal female with last period < 12 months before screening agreeing to use a highly effective form of contraception (oral, injected or implanted hormonal contraception, intrauterine device, diaphragm, condom, abstinence) during the trial and for 3 months after hydroxycarbamide discontinuation.
6. Male patients with partners of childbearing potential agreeing to use an effective contraception during the study and for 3 months after hydroxycarbamide discontinuation. Men with pregnant or lactating women should be advised to use barrier method contraception (condom) to prevent the foetus or neonate from exposure to hydroxycarbamide.
7. Patients who are covered by insurance scheme according to local regulatory requirements.

4.3 EXCLUSION CRITERIA

The exclusion criteria are to be verified at the screening and inclusion visits (V1 and V2). Patients meeting AT LEAST one of the following exclusion criteria must not be enrolled in the study:

1. Patients who had severe VOC requiring hospitalisation or ACS within the last 4 weeks preceding screening visit.
2. Patients treated with hydroxycarbamide for any reason within the previous 6 months.
3. Patients who have had chronic blood transfusion or transfusion in the last 3 months.
4. Patients with a history of hypertension (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg) treated with antihypertensive agent belonging to pharmacological class RAS inhibitor.
5. Patients who have symptoms suggestive of urinary tract infection or patients with gross haematuria.

6. Patients with a concomitant primary kidney disease.
7. Patients with any systemic condition that could result in a glomerulopathy not related to SCD (e.g. diabetes mellitus, active hepatitis B or C infections, systemic lupus erythematosus, inflammatory arthropathies).
8. Patient with a stage 3, 4 or 5 chronic kidney disease (eGFR < 60 mL/min per 1.73 m^2).
9. Patients with eGFR ≥ 140 ml/min/1,73m² (due to the lack of information regarding the magnitude, direction and significance of the trends in eGFR evolution that could be expected in this population).
10. Patients requiring long-term treatment with drugs potentially nephrotoxic (see non-exhaustive list).
11. Patients requiring ACE inhibitors or ARBs within the 3 months before inclusion regardless of the indication.
12. Patients requiring long-term treatment with non-steroidal anti-inflammatory drugs.
13. Patients who have treatment which can modify the kidney function (see non-exhaustive list) in the last 3 months.
14. Patients known to be infected with HIV.
15. Female patients who are pregnant or lactating.
16. Unreliable patients including non-compliant patients, patients with known alcoholism or drug abuse or with a history of a serious psychiatric disorder as well as patients unwilling to give informed consent or to abide by the requirements of the protocol.
17. Simultaneous participation in other clinical trials of an investigational medicinal product or previous participation within 30 days before inclusion.
18. Persons in detention by judicial or administrative decision.
19. Patients with chronic conditions that upon investigator judgment may lead to a limited life expectancy.

4.4 RANDOMISATION

Eligible patients will be randomised in a 1:1 ratio to either hydroxycarbamide or placebo. The randomisation will be stratified by baseline ACR (≤30 mg/mmol and >30 mg/mmol).

4.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory

authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals experiencing any event or condition during the screening period (screen failure) leading to exclusion from the study according to exclusion criteria of this protocol may be re-screened once the reason for exclusion is solved.

Rescreened participants will be assigned the same participant number as for the initial screening.

5. SCHEDULE OF STUDY VISITS

Study assessments will be performed from screening (V1) to end-of-study visit (V6, Month 12). Patients will attend a total of 6 visits at the clinical centre. The detail of study visits and assessments is provided hereafter and in Table 3 Flow chart of study visits and assessments.

Table 3 Flow chart of study visits and assessments

FLOW CHART OF STUDY VISITS AND ASSESSMENTS

	Pre-treatment phase		**Treatment phase**				
	Screening	**Inclusion (Randomisation)**	**Follow-up visit**	**Follow-up or End of study visit[1]**	**Follow-up Visit[2]**	**Follow-up Visit[2] End of study/**	**Early termination**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	
Schedule (month/day)	**D-30 - D0**	**D0**	**M3 D90±14**	**M6 D182±14**	**M9 D273±14**	**M12 D365±14**	
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Randomisation		X					
Demographic information	X						
Medical and surgical history	X						
Previous medication(s)[3]	X						
Concomitant medication(s) (CM)	X	X	X	X	X	X	X
Physical examination and blood pressure	X	X	X	X	X	X	X
Semen cryopreservation[4]	X						
Haematology[5]							
Blood sampling	X		X	X	X	X	X
Results		X	X	X	X	X	X
Prescription[6]		X					
Biobank blood sample[7]	X			X		X	X
Biochemistry[8]							
Blood sampling	X		X	X	X	X	X
Results		X	X	X	X	X	X
Screening for HIV, HBV, HCV							
Blood sampling	X						
Results		X					
Pregnancy test[9] for women							
Blood sampling	X						

Result		X					
Check of contraceptive use	X	X	X	X	X	X	X
Urine analysis :							
prescription and a collection kit for urine analysis	X[10]		X[10]		X[10]		
ECBU and Hematuria during 3 consecutive days	X[10]			X[10]		X[10]	X[10]
Urine albumine and urine creatinine for ACR during 3 consecutive days	X[10]			X[10]		X[10]	X[10]
Results		X[11]		X[12]		X[12]	X
Intermediate local analysis of urine albumin and urine creatinine for ACR on one day			X		X		
Biobank blood and urine sample[7]	X			X		X	X
Dispensation of study treatment[13]		X	X	X[14]	X[14]		
Compliance to study treatment			X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X
Diary cards (reporting of drug intake/AE/CM/SCD events)							
- Dispensing		X	X	X	X		
- Collection/review			X	X	X	X	X

ACR: Albumin-to-Creatinine Ratio; AE: Adverse Event; CM: Concomitant Medication; D: Day; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; M: Month; SCD: Sickle Cell Disease; V: Visit.

[1]For unresponsive patients or responsive patients unwilling to continue the study, this visit will be the End of study visit.

[2]Additional visits only for patients qualified as responders and willing to continue the study.

[3]Previous blood transfusions and previous administration of hydroxycarbamide will be reported.

[4]Not required if semen cryopreservation was already performed in the past. If semen volume or viable sperm cell amount is insufficient for cryopreservation of the collected sample, a spermogram will be performed and conserved in CECOS during the whole duration of the study. A control spermogram could be performed in patients at least 6 months and at most 9 months after the last dose of treatment.

[5]The following assessments will be performed: WBC and differential counts, platelets, MCV, MCHC, MCH, Hb, HbF, free Hb, %DRBCs, reticulocytes, endogenous EPO, and ferritin

[6]At V2, prescription will be given for hematology assessment in local lab 1 month after treatment initiation.

[7]Optional exploratory biobank: blood and urine samples for patients from French sites only.

[8]The following assessments will be performed: LDH, AST, ALT, BUN, conjugated and total bilirubin and blood creatinine for glomerular filtration rate (GFR) calculation. The CKD-EPI formula will be used for eGFR calculation. In addition, fasting glycemia and Glycated haemoglobin (HbA1c) may be assessed before V2 upon investigator decision.

eGFR (millilitres per minute per 1.73 m^2) = $141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (for women), where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1. eGRF calculation will be automated in the eCRF, based on serum creatinine level, age and sex.

[9]Pregnancy tests will be performed on blood.

[10]At V1 and V3 for all patients, and at V5 for patients qualified as responders and willing to continue the study: patients will receive a prescription and a collection kit for urine analysis. First morning urine samples will be collected between 6. 30 and 8. 30 a.m. during 3 consecutive days before V2 and V4 for all patients, and before V6 for patients qualified as responders willing to continue the study. Assessments of hematuria,

CBEU, urine albumin and urine creatinine for ACR evaluation will be performed at a local lab or at investigator's site.
[11]At V2, ACR result will be reported in the CRF and used for randomization.
[12]In case of ACR≥100 mg/mmol, a local assessment of ACR will be performed one month later to confirm ACR result. Patients will receive a prescription and a collection kit for local ACR assessment on first morning urine samples collected during 3 consecutive days.
[13]This study is double-blinded.
[14]Only for patients qualified as responders and willing to continue the study.

5.1 SCREENING VISIT (V1, D-30)

Before performing any specific study procedures, patients must have signed a written informed consent form (ICF).

The following screening assessments (Table 4) will be performed prior to the initiation of treatment, in order to verify the inclusion/exclusion criteria and to collect baseline values of the patient. The data will be reported in the electronic case report form (eCRF) for each consenting patient.

Table 4 Assessments/procedures to be performed at screening visit (V1)

Socio-demographic information	Gender, month and year of birth, continent of origin.
Medical history	– SCD genotype (beta mutation) – Assessment of SCD disease (list of organs impaired by the disease) – Other relevant medical history
Previous medications	– SCD treatment history: blood transfusions (start and end dates), hydroxycarbamide (start and end dates, last dose). – SCN treatment history: ACE inhibitors and ARBs (start and end dates).
Concomitant medications	Collection of concomitant medications received within the 30 days prior to inclusion.
Physical examination	General appearance (report any abnormal signs), body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Haematology	WBC including differential counts, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, reticulocytes, endogenous EPO, and ferritin. Optional : Blood samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Biochemistry	Creatinine (for eGFR calculation), LDH, AST, ALT, conjugated and total bilirubin, BUN. Fasting glycemia and glycated haemoglobin (HbA1c) levels upon investigator judgement
Virology	Screening for HIV, HBV and HCV
Pregnancy test (for women) and check of contraceptive use	Pregnancy tests will be performed on blood.
Semen cryopreservation	If not already done, semen cryopreservation will be done before inclusion (except for vasectomized patients). If semen volume or amount of viable cells in the collected sample is insufficient for cryopreservation, a spermogram will be performed and conserved in CECOS during the whole duration of the study. A control spermogram could be performed in patients at least 6 months and at most 9 months after the last dose of treatment.

Urinalysis	- Patients will receive a prescription for urine analysis (Hematuria, CBEU and ACR). They will also be provided with kit and guidelines for urine sample collection and storage. They will be asked to collect at home first morning urine samples on 3 consecutive days for the evaluation of ACR. Samples will be collected between 6.30 and 8.30 a.m. and the patient will bring the sample to a local laboratory of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient. The laboratory will be the same for the subsequent analyses. - Optional : Urine samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory

ACR: Albumin-creatinine ratio; ALT: Alanine Amino Transférase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBEU: Cytobacteriological examination of the urine; eGFR: estimated glomerular filtration rate; EPO; erythropoietin; Hb: Heamoglobin; HbF; Foetal haemoglobin; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; SCD: Sickle Cell Disease; WBC: White blood count; %DRBCs: percentage of dense red blood cells.

The Investigator will also explain to the patient the modalities of the treatment, and review the unauthorised treatments during the study.

5.2 INCLUSION VISIT (V2, D0)

Patients who have signed the ICF, who have successfully completed the screening visit, who meet all inclusion criteria and do not demonstrate any exclusion criteria will be included in the study and will be randomised to either hydroxycarbamide or placebo. Assessments/procedures to perform during the inclusion visit are described in Table 5.

Table 5 Assessments/procedures to be performed at inclusion visit (V2)

Concomitant medications	Collection of concomitant medications received since screening.
Physical examination	General appearance (report of any abnormal signs), body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Recording and assessment of AEs	AEs, SAEs.
Contraceptive use	Use of contraceptive will be checked.
Urinalysis	Collection of Hematuria and CBEU results.
Randomisation	Collection of ACR evaluation result for randomisation
Dispensation of study treatment by pharmacist	According to the randomisation. The study is double-blinded.
Prescription for complete hematology assessment in local lab	Complete hematology assessment will be performed in local lab 1 month after treatment initiation at least.
Diary cards	Patients will be provided with diary cards.

AE: Adverse event; ACR: Albumin-creatinine ratio; CBEU: Cytobacteriological examination of the urine; SAE: Serious Adverse event.

5.3 FOLLOW-UP VISITS

As described in the flow chart, 4 follow-up visits are planned:

- Visit 3 will be performed at the clinical centre 3 months ± 14 days after treatment initiation.
- Visit 4 will be performed at the clinical centre 6 months ± 14 days after treatment initiation.
- Visit 5 will be performed at the clinical centre 9 months ± 14 days after treatment initiation for responder patients willing to continue the study.
- Visit 6 will be performed at the clinical centre 12 months ± 14 days after treatment initiation for responder patients willing to continue the study.

Assessments/procedures to perform during these visits are described in Table 6 (V3 and V5), Table 7 (V4) and Table 8 (V6).

Table 6 Assessments/procedures to be performed at V3 and at V5 for responder patients willing to continue the study

Concomitant medications	Collection of concomitant medications received since last visit.
Physical examination	General appearance (report any abnormal signs), body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Contraceptive use	Use of contraceptive will be checked at each visit.
Haematology	WBC including differential counts, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, reticulocytes, endogenous EPO, and ferritin.
Biochemistry	Creatinine (for eGFR calculation), haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin).
Urinalysis	- Local first-morning urine albumin and urine creatinine for assessment of ACR, - CBEU, Hematuria Patients will receive a prescription for urine analysis (hematuria, CBEU and ACR). They will also be provided with kit and guidelines for urine sample collection and storage. They will be asked to collect at home first morning urine samples on 3 consecutive days for the evaluation of ACR at V4 and at V6 for responder patients willing to continue the study. Samples will be collected between 6.30 and 8.30 a.m. and the patient will bring the sample to a local laboratory of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient. The laboratory will be the same for all analyses of the patient.
Recording and assessment of AEs	Treatment-emergent AEs, SAEs, and SCD-related events.
Dispensation of study treatment	According to the randomisation. The study is double-blinded.
Compliance to study treatment	Patients will have to return the packaging of the used study treatment as well as the unused study treatment.
Diary cards	Completed diary cards will be collected and reviewed. Patients will be provided with new diary cards.

ACR: Albumin-creatinine ratio; AE: Adverse event;; ALT: Alanine Amino Transférase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBEU: Cytobacteriological examination of the urine; eGFR: estimated glomerular filtration rate; EPO; erythropoietin; Hb: Haemoglobin; HbF; Foetal haemoglobin; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; SAE; Serious adverse event; SCD: Sickle Cell Disease; V: Visit; WBC: White blood count; %DRBCs: percentage of dense red blood cells.

Table 7 Assessments/procedures to be performed at V4

Concomitant medications	Collection of concomitant medications received since last visit.
Physical examination	General appearance (report any abnormal signs), body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Contraceptive use	Use of contraceptive will be checked at each visit.
Haematology	WBC including differential counts, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, reticulocytes, endogenous EPO, and ferritin. Optional : Blood samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Biochemistry	Creatinine (for eGFR calculation), haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin).
Urinalysis	- Collection of hematuria, CBEU and ACR results. In case of omission, the patient will be reminded to collect urine samples on 3 consecutive days as early as possible. Optional : Urine samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Recording and assessment of AEs	Treatment-emergent AEs, SAEs, and SCD-related events.
Dispensation of study treatment	According to the randomisation and only for patients qualified as responders willing to continue to participate in the trial. The study is double-blinded.
Compliance to study treatment	Patients will have to return the packaging of the used study treatment as well as the unused study treatment.
Diary cards	Completed diary cards will be collected and reviewed. Patients will be provided with new diary cards.

ACR: Albumin-creatinine ratio; AE: Adverse event;; ALT: Alanine Amino Transférase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBEU: Cytobacteriological examination of the urine; eGFR: estimated glomerular filtration rate; EPO; erythropoietin; Hb: Haemoglobin; HbF; Foetal haemoglobin; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; SAE; Serious adverse event; SCD: Sickle Cell Disease; V: Visit; WBC: White blood count; %DRBCs: percentage of dense red blood cells.

Table 8 Assessments/procedures to be performed at V6 for responder patients willing to continue the study only

Concomitant medications	Collection of concomitant medications received since last visit.
Physical examination	General appearance (report any abnormal signs), body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Contraceptive use	Use of contraceptive will be checked at each visit.
Haematology	WBC including differential counts, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, reticulocytes, endogenous EPO, and ferritin. Optional : Blood samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Biochemistry	Creatinine (for eGFR calculation), haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin).
Urinalysis	Collection of hematuria, CBEU and ACR results. In case of omission, the patient will be reminded to collect urine samples on 3 consecutive days as early as possible. Optional : Urine samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Recording and assessment of AEs	Treatment-emergent AEs, SAEs, and SCD-related events.
Compliance to study treatment	Patients will have to return the packaging of the used study treatment as well as the unused study treatment.
Diary cards	Completed diary cards will be collected and reviewed.
End-of-study form	Will be completed by the Investigator.

ACR: Albumin-creatinine ratio; AE: Adverse event;; ALT: Alanine Amino Transférase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBEU: Cytobacteriological examination of the urine; eGFR: estimated glomerular filtration rate; EPO; erythropoietin; Hb: Haemoglobin; HbF; Foetal haemoglobin; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; SAE; Serious adverse event; SCD: Sickle Cell Disease; V: Visit; WBC: White blood count; %DRBCs: percentage of dense red blood cells.

5.4 EARLY TERMINATION FOLLOW-UP VISIT

In case of premature termination of the study, the patient will come for an early termination follow-up visit. The Investigator will try to collect all the information related to the end-of-study visit and the end-of-study form will be completed. Assessments/procedures to perform are described in Table 9.

Table 9 Assessments/procedures to be performed at early termination follow-up visits

Concomitant medications	Collection of concomitant medications received since last visit.
Physical examination	General appearance, body weight, height, physical examination focused on the criteria specified in the CRF.
Vital signs	Resting systolic and diastolic blood pressure, heart rate, body temperature.
Contraceptive use	Use of contraceptive will be checked at each visit.
Haematology	WBC including differential counts, platelets, MCV, MCHC, MCH, Hb, free Hb, HbF, %DRBCs, reticulocytes, endogenous EPO, and ferritin. Optional : Blood samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Biochemistry	Creatinine (for eGFR calculation), haemolysis markers (LDH, AST, ALT, BUN, conjugated and total bilirubin).
Urinalysis	- Hematuria, CBEU - Patients will receive a prescription for urine analysis. They will be asked to collect at home first morning urine samples on 3 consecutive days for the measurement of urine albumin and urine creatinine for assessment of ACR. Samples will be collected between 6.30 and 8.30 a.m. and the patient will bring the sample to a local laboratory of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient. The laboratory will be the same for all analyses of the patient. - Optional : Urine samples to identify any biomarkers predictive of SCN will be collected and sent to the central biobank laboratory
Recording and assessment of AEs	Treatment-emergent AEs, SAEs, SCD-related events.
Compliance to study treatment	Patients will have to return the packaging of the used study treatment as well as the unused study treatment.
Diary cards	Completed diary cards will be collected and reviewed.
End-of-study form	Will be completed by the Investigator.

ACR: Albumin-creatinine ratio; AE: Adverse event; ALT: Alanine Amino Transférase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBEU: Cytobacteriological examination of the urine; eGFR: estimated glomerular filtration rate; EPO; erythropoietin; Hb: Haemoglobin; HbF; Foetal haemoglobin; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; SAE; Serious adverse event; SCD: Sickle Cell Disease; V: Visit; WBC: White blood count; %DRBCs: percentage of dense red blood cells.

5.5 END OF THE STUDY

The study will be considered closed after the last patient has completed his/her last, planned, study-related visit.

6. STUDY ASSESSMENTS AND PROCEDURES

Study assessments will be performed from screening to end-of-study visit (V4, Month 6 or V6, Month 12 for patients qualified as responders willing to continue to participate in the trial) or early termination visit according to the flow-chart. Patients will attend a total of 4 (for all patients) to 6 (for responder patients willing to continue the study) visits at the clinic centre. All clinical laboratory analyses will be performed at the local laboratory, in compliance with good clinical practice and local requirements.

6.1 PHYSICAL EXAMINATION AND ASSESSMENT OF VITAL SIGNS

The following examinations and assessments will be performed at each visit:

- Vital signs: Respiratory rate, Body temperature, Heart rate and Blood pressure. Both systolic and diastolic resting blood pressure will be measured. The arm with the highest mean diastolic blood pressure at screening will be used for subsequent measurements.
- Body weight
- Height
- Physical examination

6.2 ASSESSMENT OF URINE ALBUMIN AND URINE CREATININE FOR ACR EVALUATION

Urine albumin and urine creatinine will be assessed in order to calculate ACR, according to the flowchart.

- For assessment of urine albumin and urine creatinine on 3 consecutive days, patients will be provided with guidelines on urine collection, storage and delivery procedures. They will receive a prescription for urine analysis and a kit for urine collection. They will be asked to collect at home first morning urine samples in polyethylene containers on 3 consecutive days between 6.30 and 8.30 a.m. Urine sample will be stored at room temperature until the patient brings the sample to a local laboratory of his/her choice or to the investigator’s site every day or the 3 samples on the third day at the most convenient for the patient. For one patient, the laboratory must be the same during the entire duration of the study.
- Intermediate local analysis of urine albumin and urine creatinine will be done on first-monrning urine on site or in a medical laboratory for ACR calculation, in order to better determine the dynamic of the response.
- If one of the three ACR values before randomization, at 6 or 12 months is considered to be very different from the other two values by the investigator, the patient will be asked to perfom an additional assessment of ACR in the following days.

- In case of ACR≥100 mg/mmol at 3, 6 or 9 months, an additional assessment of ACR will be performed one month later to confirm ACR result. Patients will receive a prescription and a collection kit for ACR assessment on first morning urine samples collected during 3 consecutive days. Urine sample will be stored at room temperature until the patient brings the sample to a local laboratory of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient.

6.3 ASSESSMENT OF EGFR

To date, MDRD study equation (Modification of diet in renal disease) and CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration) are the most used formula to estimate the GFR (estimated GFR or eGFR). But unfortunately these equations have been developed from creatinine level, age and body weight of the patient in general population. However SCD population is different: slim people, non-Caucasian with an increase of tubular secretion of creatinine and sometimes hyperfiltration.

CKD-EPI equation is particularly accurate to estimate high GFR values, including glomerular hyperfiltration, and thus should be recommended to screen SCD adult patients at high risk for SCD nephropathy.

The eGRF will be calculated from the serum creatinine, age, and sex of the patient using the CKD-EPI formula, which has been demonstrated to be the best method to estimate GFR in SCD patients [20]:

eGFR (millilitres per minute per 1.73 m^2) = 141 × min (Scr/k,1)$^{\alpha}$ × max(Scr/k,1)$^{-1.209}$ × 0.993^{Age} × 1.018 (for women), where Scr is serum creatinine, k is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

eGFR calculation will be automated in the eCRF.

6.4 ASSESSMENT OF HAEMATOLOGICAL AND BIOCHEMICAL PARAMETERS

Heamatological and biochemical parameters will be assessed by the local laboratory. The following assessments wil be performed according to the flowchart:

- Haematology: Red blood cell (RBC) count and Mean Corpuscular Volume, Dense Red Blood Cells (%DRBC), reticulocytes, Hemoglobin (Hb), free Hemoglobin (free Hb) and Fetal hemoglobin (HbF), Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC), hematocrit, White Blood Cell counts, neutrophils, lymphocytes,

monocytes, eosinophils, basophils and platelet counts, endogenous EPO and ferritin concentrations.

- Blood biochemistry :
  - Renal function: blood Creatinine.
  - Haemolysis biochemical markers: Lactate Deshydrogenase (LDH), aspartate aminotransferase (AST), ALT, BUN, conjugated and total bilirubin.
  - Fasting glycemia and glycated haemoglobin (HbA1c) levels upon investigator judgement

An approximate volume of 20 mL of blood will be required for the set of assays on a given day.

- Urinalysis: Hematuria and CBEU either locally, according to the flowchart.
  - For local assessment of hematuria and CBEU, patients will be provided with guidelines on urine collection, storage and delivery procedures. They will receive a prescription for urine analysis and a kit for urine collection. Urine samples will be stored at room temperature and the patient brings the sample to a local laboratory of his/her choice or to the investigator's site every day or the 3 samples on the third day at the most convenient for the patient.Intermediate analysis of hematuria and CBEU will be performed locally.

6.5 SEROLOGICAL ASSESSMENT

Screening for HIV, HBV, HCV will be performed on blood samples. An approximate volume of 2.5 mL of blood will be required for the set of assays on a given day.

6.6 PREGNANCY TEST

A pregnancy test will be performed on blood at screening. An approximate volume of 2.5 mL of blood will be required for the set of assays on a given day.

6.7 SEMEN CRYOPRESERVATION

Semen cryopreservation will be performed between screening and inclusion visit.

If semen volume or amount of viable cells in the collected sample is insufficient for cryopreservation, a spermogram will be performed and conserved in CECOS during the whole study duration. A control spermogram could be performed in patients at least 6 months and at most 9 months after the last dose of treatment.

6.8 ASSESSMENT OF ADVERSE EVENTS

Adverse events experienced during the trial will be recorded both in the source documents and in the eCRF. Patients will be asked to document all experienced medically relevant events in the patient diary. Events reported in the patient diary cards will be reviewed by the investigator at each visit. In addition, patients will be queried at each visit about the medical events experienced.

SCD-related events will be recorded at each visit.

Treatment-emergent adverse events (AEs) and serious AEs (SAEs) will be assessed at V2 (inclusion), V3 (Month 3), V4 (Month 6), V5 (Month 9) and V6 (Month 12). Full details of safety assessments are presented in Section 8.

6.9 OPTIONAL BIOBANK

A biobank of patient's sera blood and urine samples will be created. Urine samples (in protease inhibitor-containing tubes) and blood samples (1 heparin and 1 EDTA tubes) will be collected at V1 (Screening), V4 (Month 6) and V6 (Month 12) on patients having given written informed consent (ICF) for sample collection, storage and use for the BIOBANK exploratory analyses. Urine and sera blood will be processed, aliquoted and stored until 15 years after the end of the study (Last Patient Last Visit). Of note, sample collection at V6 will only be performed for patients qualified as responders willing to continue to participate in the trial.

The precise analyses that will be performed on these samples will depend on advances in the identification of SCN mechanisms and biomarkers until the end of the SIKAMIC trial. Unused samples will be destroyed 15 years after the end of the study.

7. STUDY TREATMENTS

7.1 RATIONALE FOR DOSE SELECTION

According to the EU label, the posology should be based on the patient's bodyweight and the recommended starting dose is 15 mg/kg bw/day. In a recent cohort study, this dose was found to significantly lessen urine ACR in SCD adult patients with microalbuminuria treated for 6 months with hydroxycarbamide [17]. The median hydroxycarbamide dose reported by authors at month 6 was 15 [12–18] mg/kg bw/day.

Therefore, in the present study, hydroxycarbamide will be prescribed at a dose of 15 mg/kg bw/day in line with label recommendations and previous works in the field.

7.2 DOSE ADJUSTMENT AND TEMPORARY INTERRUPTION

Possible adjustments of daily dose may be needed:

- If blood counts are within the toxic range (neutrophils < 1,500/mm³, platelets < 80,000/mm³, haemoglobin < 4.5 g/dL, reticulocytes < 80,000 mm³ if haemoglobin concentration < 9 g/dL), the treatment will be temporarily discontinued until blood counts recover or the dose reduced, upon investigator's judgement. The dose may be reduced to 12.5 mg/kg bw/day or 10 mg/kg bw/day. In case of treatment discontinuation, treatment may then be reinstituted at a reduced dose of 12.5 mg/kg bw/day or 10 mg/kg bw/day, upon investigator's judgement.

Administration Schedule :

The tablet(s) will be taken once daily, preferably in the morning before breakfast, where necessary, with a glass of water or a very small amount of food.

Patients assigned to the placebo group will receive placebo tablets according to the same schedule as patients in the hydroxycarbamide group.

7.3 IDENTITY OF STUDY TREATMENTS

Both hydroxycarbamide and placebo will be formulated and supplied as identical tablets concerning the colour, size and shape. They will be packed in identical plastic bottles.

Hydroxycarbamide group

Name of the medicinal product: Siklos® 100 mg or 1000 mg film-coated tablets.

Active ingredient: hydroxycarbamide 100 mg or 1000 mg.

Excipients: sodium stearyl fumarate, silicified microcrystalline cellulose and basic butylated methacrylate copolymer.

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents. Anatomical Therapeutic Chemical (ATC) code: L01XX05.

Pharmaceutical forms:

Siklos® 100 mg: off-white oblong-shaped, film-coated tablet with half-scoring on both sides.

Siklos® 1000 mg: off-white, capsule-shaped, film-coated tablet with triple scoring on both sides.

Dosage: 15 mg/kg bw/day, tablet(s) taken preferably in the morning before breakfast.

Route of administration: oral.

Special precautions for storage: do not store above 30°C.

Manufacturer: Delpharm

Placebo group

Composition: sodium stearyl fumarate, sodium starch glycolate (type A), silicified microcrystalline cellulose and basic butylated methacrylate copolymer.

Pharmaceutical forms: placebo tablets formulated to be identical in appearance to Siklos® 100 mg or 1000 mg.

Route of administration: oral.

Special precautions for storage: do not store above 30°C.

Manufacturer: Delpharm

7.4 SUPPLY AND STORAGE CONDITIONS OF THE STUDY PRODUCTS

The study products will be manufactured, tested, handled, and stored in accordance with Good Manufacturing Practice (GMP) requirements for clinical trials and used in accordance with the protocol.

The study products will be sent to the pharmacy of centre with the appropriate documents. As soon as the pharmacist receives the study products, she/he must fill in and sign the acknowledgement of receipt form in the IWRS. A copy must be kept with the Pharmacist for his/her study file and the original must be returned to the Sponsor.

The treatments must be stored in a dry, secured area, at room temperature and will be under the direct responsibility of pharmacist at that study centre. None of the study products should be stored above 30ºC. Study treatments will be dispensed by the Pharmacist at V2 (D0, inclusion), and V3 (Month 3). Dispensation will also be done at V4 (Month 6) and V5 (Month 9) for patients qualified as responders willing to continue to participate in the trial.

The Pharmacist is required to keep appropriate documentation of the delivery, use and destruction, or the return of unused, used or partially used packages of study products. The documentation must include dates, quantities, patient numbers, batch/serial numbers or other identification number, expiry dates and the means to identify the patient to whom it was given.

All treatments supplied by the Sponsor and given to the pharmacy must be adequately accounted for during periodic monitoring visits as the study progresses. All study products, used or unused, will be destroyed by the centre at the end of the study.

7.5 PACKAGING AND LABELLING OF THE STUDY PRODUCTS

The study products will be labelled in accordance with GMP requirements for clinical trials. All the procedures to keep the blind conditions as well as the packaging and labelling procedures will be conducted by Creapharm.

The study products will be packaged in plastic bottles of 60 tablets of 100 mg and 30 tablets of 1000 mg.

7.6 CONCOMITANT TREATMENTS

7.6.1 Authorised medications during the study

Concomitant medication, as long as it is not mentioned under Section 4.3, is allowed but has to be documented in the eCRF. Information to be provided are: trademark or International Non-proprietary Name, route, dose, frequency, reason for therapy, date of onset and of cessation. The patient should not take any concomitant treatment without the Investigator's knowledge.

7.6.2 Unauthorised medications during the study

The following concomitant medications that might interfere with the clinical results are prohibited over the course of the study:

7.6.2.1 Patients who have treatment which can modify the kidney function (see non-exhaustive list) in the last 3 months.

The drugs listed below may have direct action on kidneys and could modify parameters of evaluation of renal function (*e.g.* diuretics, NSAIDS…). For this reason, the use of these drugs must be limited or preferably stopped before the enrolment of the patient. This list is not exhaustive and any drug which could potentially act on renal function must be avoided.

- ACE inhibitors or ARBs (prohibited except in a rescue way).
- NSAIDs: in case of NSAID therapy, treatment should be discontinued at least for the 15 days prior to any urine sample collection for ACR assessment.
- Any other treatment that might alter kidney function: their use must be restricted and taken into consideration at the start and all along the study.
  - Diuretics
  - Sartans
  - Aliskiren
  - Sacubitril/valsartan
  - Gliflozin drugs

7.6.2.2 Nephrotoxic drugs (most of these medicines are indicated for the treatment of chronic diseases which are among the exclusion criteria of the study):

The drugs listed below may potentially causes renal damages. These medicines must not be used during the study

- Antibiotics : aminosides, vacomycin, dalbavancin, teicoplanin, telavancin, cefalotin, polymyxins, fluoroquinolones, sulfamides
- Antifungals : Amphotericin B, voriconazole
- Antivirals : tenofovir, adefovir, aciclovir, valaciclovir, famciclovir, ganciclovir, cidofovir, foscarnet
- Antiparasitics : pentamidine
- Platinum-derivatives : carboplatine, cisplatine, oxaliplatine

- Other chemotherapeutic agents : ifosfamide, raltitrexed, eribulin, cabazitaxel, aldesleukin, sorafenib
- Immunosuppressive agents : cyclosporine, tacrolimus, sirolimus, everolimus
- Intravenous immunoglobulin (IVIG) products, especially IVIG products stabilized with sucrose
- Iron-chelating agents : deferasirox, deferoxamine
- osmotic agents : mannitol
- Mood stabilizers : lithium
- Iodinated contrast agents
- Antiplatelet agents : ticagrelor, cangrelor
- Antilipemic agents : fibrates
- Blood glucose lowering drugs : exenatide, dulaglutide, liraglutide

This list of medication is not exhaustive and the investigator should ensure that nephrotoxicicity is not among the side effects of any medicine prescribed during the course of the study.

7.7 COMPLIANCE

Subject compliance will be critical and will therefore be monitored in multiple ways.

Patients will receive instructions and guidelines about the medication intake procedure and will be required to report on a diary card any deviation to the treatment administration schedule.

At each visit after inclusion (V2, D0), the patient will be asked to bring back the bottles of the test drug used during the previous study period. The study centres will verify the treatment compliance by counting the number of placebo or hydroxycarbamide tablets left from the previous visit and by reviewing information recorded in the diary card and will document these quantities in the appropriate section of the eCRF.

Patients will be regarded as compliant if the calculated compliance is at least 80% of the study medication required to be taken during the study, unless a dose is withheld due to AEs or other unavoidable reasons (requires approval by the Investigator). Patients deemed to be non-compliant will be withdrawn from the study and the end-of-study form will be filled out.

8. ADVERSE EVENTS

8.1 DEFINITIONS

ADVERSE EVENT (AE)

According to International Conference on Harmonisation (ICH) Guideline, an **AE** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign

(including an abnormal laboratory finding), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product.

SERIOUS ADVERSE EVENT (SAE)

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility (see exceptions below).
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly/birth defect:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity).

Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Exceptions:

- Planned hospitalization for medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status documentation (*e.g.*: routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry in study trial; appropriate documentation required)
- Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

SAFETY ISSUES

All unexpected events that might materially influence the benefit-risk assessment of the medicinal product or that would lead to changes in the administration of a medicinal product, in overall conduct of a clinical trial, in the study documents.

Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity), a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor.

8.2 COLLECTION AND ASSESSMENT OF ADVERSE EVENTS BY THE INVESTIGATOR

The investigator will monitor each patient for AEs on a routine basis throughout the study. The investigator will assess and record any SAE data in detail, including the date of onset, description, severity, duration and outcome (when known), relationship of the event to the study drug, an event diagnosis, if known, and any action(s) taken.

Whenever possible, diagnosis or syndrome name should be preferred to symptoms. For all AEs, the investigator must seek to obtain all the information in order to adequately

determine the outcome of the AE and assess whether it meets the criteria for classification as an SAE as well as to determine causal relationship.

8.2.1 Seriousness

Refer to the definition given in Section 8.1. (Serious adverse event)

8.2.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

The term ‘severe’ is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as ‘serious’, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory obligations.

8.2.3 Relationship to investigational product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

At least a reasonable Possibility	The temporal relationship of the AE to study treatment administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
No Reasonable Possibility	The temporal relationship of the AE to study treatment administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

8.2.4 Action taken with study treatment

The Investigator will report the dose reduction, dose interruption, or study treatment discontinuation (if any) following an AE. He/she will also report the addition of other medications to treat the AE.

8.2.5 Outcome

At the time of the last observation, the Investigator will classify the event as:

- **Resolved:** The AE is no longer present at any intensity – symptoms have completely abated.
- **Resolving:** The AE is being resolved
- **Resolved with sequelae:** The AE is resolved but has resulted in consecutive symptom(s) or has not returned to baseline.
- **Not resolved:** The AE has not resolved, but is still present with the same intensity.
- **Fatal:** This AE directly caused or contributed to patient´s death.
- **Unknown:** There is no information available on the outcome of the event.

8.2.6 Laboratory test abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF. When capturing AE laboratory abnormalities, the clinical, rather than the laboratory term should be used by the reporting investigator wherever possible (e.g., anemia versus low hemoglobin value) and graded according to the NCI CTCAE v 4.0. Laboratory abnormalities corresponding to grades 3, 4, 5 should be considered serious and reported by the investigator to the sponsor as SAEs under the timelines defined in the next section.

Exception:
In the context of this study, neutropenia with polymorphonuclear neutrophil count > 1.5 x 10^9/L should not be considered as SAE (see also section 8.3.2 below).

8.3 REPORTING OF ADVERSE EVENTS AND SAFETY ISSUES BY THE INVESTIGATORS

8.3.1 Serious adverse events (SAEs) and safety issues

The investigator shall notify the sponsor, immediately on the day of awareness, of any SAE or safety issue if it occurs:

- from the date of consent signature,
- throughout the duration of the follow-up period of the subject.

Any patient excluded from the study due to a SAE will be followed at the same rate as the other patients.

TYPE OF EVENT	NOTIFICATION PROCEDURES	TIME TO NOTIFICATION OF SPONSOR
Non-serious AE	In the case report form	No immediate notification
Serious AE	Initial SAE declaration form + written report, if necessary	**Sponsor notified immediately**
Safety issue	Declaration form + written report, if necessary	**Sponsor notified immediately**
Pregnancy	Pregnancy declaration form	As soon as pregnancy is confirmed

The forms must be sent to the sponsor:
ADDMEDICA
pv@addmedica.com
16 rue Montrosier
92200 Neuilly-sur-Seine
Tel: +33 (0)1 72 69 01 86
http://www.addmedica.com

All these events (SAE or safety issue) must be followed until they are fully resolved. Additional information (additional declaration form) concerning the outcome of the event, if not mentioned in the first report, will be sent to the Sponsor by the Investigator.
The occurrence of pregnancy during the period or immediately after a clinical trial, is not a SAE. However, a pregnancy must be notified within the same timelines as a SAE as it will have a special follow-up until its full term. Any anomaly observed in the foetus or the child will then be notified. Any voluntary abortion, medical abortion or spontaneous abortion requires a pregnancy notification and if it requires hospitalisation, it must be transmitted according to the same procedure as a SAE.

8.3.2 Non serious adverse events

The Investigator will report all the AEs on the AE form of the eCRF. The start date, actions undertaken, and outcome must be reported, and the Investigator must evaluate the events in terms of severity, intensity, and causality with respect to the study treatment.

Exception: in the context of this study, as it is a well-known undesirable effect of Siklos® described in the SmPC, neutropenia with polymorphonuclear neutrophil count > 1.5 x 10^9/L **should not be considered serious**.

8.3.3 Reporting of adverse events and safety issues after study closeout or termination

The Investigator should also notify the Sponsor of any serious adverse events related to the study product occurring at any time after a subject has discontinued or terminated study participation.

8.4 REPORTING OF SUSARS AND SAFETY ISSUES BY THE SPONSOR

Suspected unexpected serious adverse reactions (SUSARs) will be reported by the sponsor to the French National Competent Authority (ANSM) and the Eudravigilance Clinical Trial Module (EVCTM) within the following timelines:

- Immediately (ANSM) after knowledge by the sponsor for "fatal and life-threatening" events, and follow-up information is subsequently communicated within an additional 8 days
- All other suspected serious unexpected adverse reactions shall be reported to the ANSM and EVCTM as soon as possible but within a maximum of 15 days of first knowledge by the sponsor

The sponsor informs the ANSM and the Ethics Committee of safety issues and measures taken, as applicable.

9. DATA HANDLING

9.1 CASE REPORT FORM

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported by signing the eCRF.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, expected adverse reactions data and clinical laboratory data will be entered into the eCRF, a 21 CFR Part 11-compliant web-based data capture system provided by ICTA (Dijon, France), on an ongoing basis right after patient's visits. The data will be stored on ICTA's server for 20 years and returned to sponsor on demand.

The following data will be directly uploaded from IWRS to the eCRF:

- ACR baseline level (≤ or >30 mg/mmol),
- Planned and actual treatment batch number,
- Actual date of treatment dispensation.

The data capture system includes password protection and internal quality checks, such as automatic checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The eCRF modules will be designed by ICTA's Data Management Department and developed by ICTA's Information Technology Department in accordance to CDASH (CDISC) whenever possible.

9.2 DATA MANAGEMENT

SAS® software version 9.2 or later will be used for data management process and data will be recorded in the clinical database stored in a secured folder.
The Data Management Department of ICTA (Dijon, France) is responsible for data processing including drafting of the Data Management Plan, development of the database structure, drafting of the Data Validation Plan (list of edit checks and cleaning listings), data transfer(s) and data coding: medical history and adverse events will be coded using the latest available version of the MedDRA at the time of coding. Prior and concomitant medications will be coded using World Health Organization (WHO) drug dictionary (last version available).
A review of the data will be performed according to the CRO standard operating procedure. Database status will be declared as final when all data has been entered, cleaned by the Data Manager, validated by the monitor and the investigator or delegate. After declaration of a final database, the data will be exported from the SQL database to SAS datasets and both the database and the SAS datasets will be locked and protected from changes. All statistical analyses for the final analysis will be performed on the locked SAS datasets.

10. STATISTICS

10.1 GENERAL STATISTICAL CONSIDERATIONS

An overview of study analyses is included in this section. The detailed methodology of the statistical analyses will be documented in a statistical analysis plan (SAP). The SAP will be written by the Clinical Research Organisation (CRO) in charge of the study and will be validated by the Sponsor prior to performing the analysis. The SAP must be signed before the database lock.

Quantitative variables will be presented in terms of count, mean, standard deviation, median, first and third quartiles (Q1 and Q3), and range (minimum and maximum values), and corresponding 95% confidence intervals (CIs).

For qualitative variables, the number and percentage of patients in each category will be reported with corresponding CIs where applicable.

All efficacy analyses will be adjusted by stratification factors. If one or more strata appear to have few patients for analysis, small strata will be pooled together. The method will be described in the SAP.

Patient dispositions, protocol deviations, demographic and baseline characteristics will be summarized using descriptive statistics.

Individual patient listings will be provided and graphical presentations will be provided for selected endpoints.

Analyses will be performed using SAS® software version 9.2 or higher.

10.2 SAMPLE SIZE

According to the primary endpoint, a responder is defined as a patient achieving at least a 30% decrease of the ACR baseline at 6 months. Assuming a 1:1 treatment allocation ratio, the sample size of 86 evaluable patients will achieve 80% power to detect an absolute difference of 25% in responder rates (35% in the Hydroxycarbamide group and 10% in the Placebo group) using a Chi-2 test with the normal approximation method.

The 2-sided significance level is set at 5%.

Assuming that around 10% of randomised patients will not be evaluable for the primary outcome measures, 96 patients (48 in each group) should be randomised in this study.

10.3 ANALYSIS POPULATIONS

The statistical analyses will be based on the modified intention-to-treat (mITT), per protocol (PP) and safety populations, with the mITT population used for the primary efficacy analysis.

The modified Intent-To-Treat (mITT) population is defined as all randomised patients who received at least one dose of the study medication and with at least one assessment post-baseline of the primary efficacy measure.

The Per-Protocol (PP) efficacy population is defined as all patients from the mITT population without any major protocol deviation.

The safety (SAF) population is defined as all randomised patients who received at least one dose of the study medication.

10.4 EFFICACY ANALYSIS

To control the familywise Type I error rate for the evaluation of the efficacy endpoints, the secondary endpoint, absolute mean changes from baseline in eGFR, will be statistically tested at the two-sided 0.05 significance level only if the primary efficacy endpoint is statistically significant at the 2-sided 0.05 significance level. If the primary endpoint does not reach statistical significance, the planned analysis for this secondary analysis will be

considered as exploratory with a descriptive p-value and no conclusion of significance can be determined.

The primary efficacy population will be mITT.

10.4.1 Primary endpoint

The responder rate (ie. percentage of patients achieving at least 30% decrease of the ACR baseline value at 6 months) will be provided in each group with its 95% confidence interval.

Patients requiring a therapeutic change from HC to ACE or ARB inhibitors will be considered as non-responder. Patients with no ACR measure at 6 months will be considered as non-responder. A sensitivity analysis will be done with a Last Observation Carried Forward (LOCF) imputation for patients with no measure at 6 months and no requirements for a therapeutic change. Other sensitivity analyses might be defined in the SAP.

Both treatment groups will be compared using a Cochran-Mantel-Haenszel method with the stratification variable (ACR baseline ≤30 vs >30 mg/mmol) as adjusted factor. Hypothesis testing will be performed at the two-sided 5% significance level. The 95% confidence interval of the difference between the groups will be also provided. The mITT population will be the main population of analysis for this criterion.

10.4.2 Secondary endpoints

Each secondary efficacy criterion will be summarised at each time point using descriptive statistics.

If the primary endpoint is statistically significant, then the secondary endpoint, absolute mean changes from baseline in eGFR, will be tested at the 5% significance level. An Analysis of Covariance (ANCOVA) with treatment group and baseline eGFR as fixed effects will be performed. For patients with missing value, a Multiple Imputation method will be used. Details to implement this approach will be provided in the SAP.

All other secondary endpoint testing will be considered as exploratory.

10.5 SAFETY ANALYSIS

This analysis will be performed on the safety population.

Only Treatment-Emergent Adverse Events (TEAEs), defined as any AE with an onset date on or after the first dose of study treatment or any ongoing event that worsens after the date of the first dose of study treatment, will be analysed. Other Adverse Events will be listed.

The incidence of overall TEAEs, Drug-Related TEAEs, SAEs, Grade 3-4 of TEAEs, and TEAEs leading to dose reduction or treatment discontinuation will be provided in each treatment group and overall during the first 6 month-period. Both treatment groups will be

descriptively summarised by System Organ Class (SOC) and Preferred Terms (PT) and compared using a Chi-2 (or a Fisher Exact test, if the Chi-2 conditions of application are not met) at two-sided 5% significance level.

The incidence of overall TEAEs, Drug-Related TEAEs, SAEs, Grade 3-4 of TEAEs, and TEAEs leading to dose reduction or treatment discontinuation will also be provided from month 6 to month 12 in each treatment group and overall for patients qualified as responders willing to continue the study.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for the classification of AEs. This will permit to describe the incidence of above AEs by System Organ Class and Preferred Term.

Other safety endpoints such as vital signs and laboratory data will be descriptively summarised.

11. ETHICAL AND REGULATORY ASPECTS

11.1 STUDY CONDUCT

This study will be conducted in accordance with all applicable regulatory requirements including the general ethical principles outlined in the Declaration of Helsinki, Fortaleza, October 2013 and in compliance with this protocol, the requirements of ICH Harmonised Guideline E6(R2) – Guideline for Good Clinical Practice, t. as well as any European and/or local applicable laws and regulations relating to the conduct of the study.

11.2 COMPETENT AUTHORITIES AND ETHICS COMITTEES

This protocol and other documents (e.g. Investigator's Brochure, Patient Information, etc.) will be submitted by the Sponsor/CRO to an IEC/IRB and competent local authorities. Before starting the study, the investigator must have received written approval of the Study Protocol and the Patient Information Consent Form from the IEC/IRB and the competent local authorities.

The IEC/IRB and the competent local authorities approval must reveal the Study Protocol version as well as the documents reviewed.

11.3 AMENDMENTS

Changes to any aspect of the study, such as modification(s) of the protocol, the written ICF, the written information provided to patients, and/or other procedures will be made only with the agreement of the Sponsor and must be submitted to the CPP and Competent Authorities for approval. With the exception of an amendment needed to eliminate hazards

to the patients in the study, all substantial amendments may only be put into practice once written approval from the CPP and Competent Authorities has been obtained.

11.4 PATIENT INFORMED CONSENT

Prior to a patient's participation in the study, written informed consent must be obtained after the Investigator has fully informed the patient of all pertinent aspects of the study. The patient must be given sufficient time to consider the information and the opportunity to ask questions and have those questions answered. The ICF must be signed and personally dated by the patient and by the Investigator according to ICH GCP. The patient must receive a copy of the signed and dated ICF and any other written information provided to the patients.

Any change to the information sheet and the consent form constitutes a substantial amendment and must be submitted for approval to the CPP and Competent Authorities.

The new ICF must be signed and personally dated by the patient and by the Investigator and the patient must receive a copy of this signed and dated ICF.

Prior to their participation in this study, patients will receive a complete and most recent approved version of the patient's information sheet (in easily comprehensible terms) and an ICF. The objectives, methods, and duration of participation, the main limitations of the protocol, and the possible risks incurred will be specified. The patient is reminded that he/she can refuse to take part in this study and can, at any time and without personal prejudice, withdraw his/her consent.

For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical study, necessary for the transcription and the verification of the collected data.

Examples of these original documents and data records include concomitant medication forms, laboratory reports, patients diaries, records of AEs and follow-up of AEs, and study treatment accountability records.

According to GCP guidelines, upon request of the Clinical Research Associate (CRA), auditor, or Competent Authority, the Investigator must provide direct access to all requested source data/documents.

Source documents along with all other study-related documents (copies of all ICFs, eCRFs CD-ROM, any correspondence related to the study…) must be kept in the Investigator's

file throughout the study, and then, must be stored in the study centre's archives of at least 15 years as per the European Directive 2003/63/ EC and according to local legal requirements.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 STUDY MONITORING

In accordance with applicable regulations, GCP, and CRO standard operating procedures, an initiation visit will be performed at the study centre before any patients are included in the study. The aim of this visit is to review the protocol and data collection procedures with the study personnel as well as to provide a reminder of the Investigator's responsibilities according to ICH GCP.

During the study, the CRA will regularly contact the centre and will perform on-site monitoring visits. The extent, nature, and frequency of on-site visits will be based on the patient inclusion rate and will be discussed with the Investigator. The aim of these contacts and visits is to check the progress of the study, review all the collected study data, conduct source document verification, identify any issues and address their resolution. This will be done in order to verify that the data are authentic, accurate and complete, the safety and rights of patients are being protected, and the study is being conducted in accordance with the approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator agrees to allow the CRA direct access to all relevant documents and to allocate his/her time and the time of the study personnel to discuss any issues.

Upon completion of the study, the CRA, with the collaboration of the Investigator, will ensure that:

- All data queries have been finalised,
- The centres' study records are complete.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) which describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

13.2 AUDIT AND INSPECTION

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or a CRO designated by the Sponsor may conduct a quality assurance audit of the investigator centre. Regulatory Agencies may also conduct regulatory inspections. Such audits or inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator centre agrees to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of the study personnel to the auditor/inspector to discuss findings and any relevant issues.

14. CONFIDENTIALITY, DATA HANDLING, AND RECORD KEEPING

14.1 PERSONAL DATA PROTECTION AND CONFIDENTIALITY

All relevant legislation on Data Protection will be followed. Information regarding patients' identity obtained as a result of this study is considered confidential and disclosure to unauthorised individuals is prohibited.

Patients will not be identified by their names or date of birth. As soon as they have signed their ICF, patients will be given a unique identification number that will be used throughout the study. Patients will be identified with centre number and patient number in the eCRF. In all other documents and materials, patients will only be identified with a patient identification code (centre number and patient number).

According to GCP requirements, the Investigator will maintain a 'patient identification log' with the name and contact details of each patient. This log and the signed consent forms will be kept in strict confidence by the Investigator.

The patients will be informed by the information and consent form that their personal data collected for the purpose of the study will be kept confidential and will be processed by the Sponsor and its representatives. The patients will also be informed of their rights according to General Data Protection Regulation and French law.

14.2 RECORD KEEPING

The investigator undertakes to adequately maintain all study documentation and records to ensure full documentation of the study conduct and enable subsequent verification of study data.

Following closure of the study, the Investigators must archive, in a safe and secure location, all study records including patient medical files, original ICFs, source documents, eCRFs CD-ROM, copies of the study product accountability forms, copies of the CPP/regulatory authorities' approval, and all correspondence. The trial-related documents must be retained as strictly confidential at the Investigator's centre for at least 15 years according to the European Directive 2003 / 63 / EC and local legal requirements. The Investigator or his/her institution should take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor of any changes in the archiving arrangements, including, but not limited to: archival at an off-site facility and transfer of ownership of the records in the event the Investigator leaves the site. The Investigator must obtain Sponsor written permission before disposing of any records, even if retention requirements have been met.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or CPP imposes shorter time limits.

15. INSURANCE AND FINANCES

15.1 INSURANCE

The Sponsor, ADDMEDICA S.A.S., certifies that a medical insurance policy (with HDI Global SE, Tour Opus 12 La défense 9, 77 Esplanade du Général de Gaulle F92914 Paris la Défense Cedex - policy number : 01013166-14003) has been taken out, which covers the liability of the Investigator in case of damage or injury resulting from this study, in accordance with Articles 3.2 and 6.3 of Directive 2001/20/EC of the European Parliament.

This insurance does not relieve the Investigators of any obligation to maintain their own liability insurance policy as required by applicable law.

15.2 FINANCES

The funding of research is supported by the Sponsor (investigator time, study costs, patients compensation for travel expenses…).

ADDMEDICA S.A.S. will fairly compensate the centre/the principal investigator for conducting the clinical study. The rate of compensation will take into account factors such as required procedures, time commitment, and study complexity.

According to French national law (article L.4113.6 of the French Health Code):

- The financial agreement related to the study will be submitted for opinion to the CNOM (French National Medical Order) and the investigator will then transmit to the CDOM (French Departmental Medical Order) the financial agreement with the letter of submission to the CNOM for information
- The sponsor will inform the CNOM of the agreement implementation.

According to the 2011-2012 French law dated December 29, 2011 and its implementing decree 2013-414 of 21 May 2013, the sponsor will publish the existence of this agreement as well as benefits in kind or in cash providing directly or indirectly to the investigator.

15.3 PATIENT PAYMENTS AND EXPENSES

Patients will not be paid for participating in the study but their travel expenses will be reimbursed.

16. PUBLICATION POLICY

All the results of this study are the property of the Sponsor and have to be considered as confidential.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results is drawn up according to ICH

Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95). Global results of the research are communicated to the Investigators. According to the local regulation, the patient can ask the Investigator for the results.

The Sponsor acknowledges the importance of publication of information collected or generated for this study by the study sites. Final data will be appropriately communicated when available, through presentation at national and/or international congresses. Final results of this study will also be submitted for review and publication to an appropriate scientific and medical journal. Authorship of any publications relating to the study shall be determined by mutual agreement and will follow the International Committee of Medical Journal Editors (ICMJE) guidelines.

Additionally, this study and its results may be submitted for inclusion in all appropriate Health Authority study registries.

17. REFERENCE LIST

1. Falk RJ, Scheinman J, Phillips G*, et al.* Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. N Engl J Med. 1992 Apr 2;326(14):910-5.
2. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005 Nov;84(6):363-76.
3. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal Failure in Sickle Cell Disease: Prevalence, Predictors of Disease, Mortality and Effect on Length of Hospital Stay. Hemoglobin. 2016 Sep;40(5):295-9.
4. McClellan AC, Luthi JC, Lynch JR*, et al.* High one year mortality in adults with sickle cell disease and end-stage renal disease. Br J Haematol. 2012 Nov;159(3):360-7.
5. Platt OS, Brambilla DJ, Rosse WF*, et al.* Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994 Jun 9;330(23):1639-44.
6. Maigne G, Ferlicot S, Galacteros F*, et al.* Glomerular lesions in patients with sickle cell disease. Medicine (Baltimore). 2010 Jan;89(1):18-27.
7. Ataga KI, Derebail VK, Archer DR. The glomerulopathy of sickle cell disease. Am J Hematol. 2014 Sep;89(9):907-14.
8. Becker AM. Sickle cell nephropathy: challenging the conventional wisdom. Pediatr Nephrol. 2011 Dec;26(12):2099-109.
9. Sharpe CC, Thein SL. Sickle cell nephropathy - a practical approach. Br J Haematol. 2011 Nov;155(3):287-97.
10. Sharpe CC, Thein SL. How I treat renal complications in sickle cell disease. Blood. 2014 Jun 12;123(24):3720-6.
11. Zhang F, Liu H, Liu D*, et al.* Effects of RAAS Inhibitors in Patients with Kidney Disease. Curr Hypertens Rep. 2017 Aug 8;19(9):72.
12. Voskaridou E, Terpos E, Michail S*, et al.* Early markers of renal dysfunction in patients with sickle cell/beta-thalassemia. Kidney Int. 2006 Jun;69(11):2037-42.

13. Foucan L, Bourhis V, Bangou J*, et al.* A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia. Am J Med. 1998 Apr;104(4):339-42.
14. Quinn CT, Saraf SL, Gordeuk VR*, et al.* Losartan for the nephropathy of sickle cell anemia: A phase-2, multicenter trial. Am J Hematol. 2017 Sep;92(9):E520-E8.
15. Haymann JP, Hammoudi N, Stankovic Stojanovic K*, et al.* Renin-angiotensin system blockade promotes a cardio-renal protection in albuminuric homozygous sickle cell patients. Br J Haematol. 2017 Dec;179(5):820-8.
16. Segal JB, Strouse JJ, Beach MC*, et al.* Hydroxyurea for the treatment of sickle cell disease. Evid Rep Technol Assess (Full Rep). 2008 Mar(165):1-95.
17. Bartolucci P, Habibi A, Stehle T*, et al.* Six Months of Hydroxyurea Reduces Albuminuria in Patients with Sickle Cell Disease. J Am Soc Nephrol. 2015 Nov 19. Eng.
18. Laurin LP, Nachman PH, Desai PC, Ataga KI, Derebail VK. Hydroxyurea is associated with lower prevalence of albuminuria in adults with sickle cell disease. Nephrol Dial Transplant. 2014 Jun;29(6):1211-8.
19. KDIGO. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2012;3(1).
20. Arlet JB, Ribeil JA, Chatellier G*, et al.* Determination of the best method to estimate glomerular filtration rate from serum creatinine in adult patients with sickle cell disease: a prospective observational cohort study. BMC Nephrol. 2012 Aug 6;13:83.
21. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015 Mar;11(3):161-71.
22. Biemond B, Elsita W, Van Tuijn C, Nur E, Vogt L. Predictive Value of Gradual Change in Renal Function on Vasculopathy Related Complications and Mortality in Patients with Sickle Cell Disease. Blood. 2017;130.
23. Kato GJ, Piel FB, Reid CD*, et al.* Sickle cell disease. Nat Rev Dis Primers. 2018 Mar 15;4:18010.
24. Abdu A, Gomez-Marquez J, Aldrich TK. The oxygen affinity of sickle hemoglobin. Respir Physiol Neurobiol. 2008 Mar 20;161(1):92-4.
25. Li X, Dao M, Lykotrafitis G, Karniadakis GE. Biomechanics and biorheology of red blood cells in sickle cell anemia. J Biomech. 2017 Jan 4;50:34-41.
26. Piel FB, Patil AP, Howes RE*, et al.* Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013 Jan 12;381(9861):142-51.
27. Chonat S, Quinn CT. Current Standards of Care and Long Term Outcomes for Thalassemia and Sickle Cell Disease. Adv Exp Med Biol. 2017;1013:59-87.
28. Charache S, Terrin ML, Moore RD*, et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995 May 18;332(20):1317-22.
29. Steinberg MH, Barton F, Castro O*, et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003 Apr 2;289(13):1645-51.
30. Steinberg MH, McCarthy WF, Castro O*, et al.* The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol. 2010 Jun;85(6):403-8. eng.

31. Di Maggio R, Hsieh MM, Zhao X*, et al.* Chronic Administration of Hydroxyurea (HU) Benefits Caucasian Patients with Sickle-Beta Thalassemia. Int J Mol Sci. 2018 Feb 28;19(3).
32. Ballas SK. Comorbidities in aging patients with sickle cell disease. Clin Hemorheol Microcirc. 2018;68(2-3):129-45.
33. Alhwiesh A. An update on sickle cell nephropathy. Saudi J Kidney Dis Transpl. 2014 Mar;25(2):249-65.
34. Miller ST, Wang WC, Iyer R*, et al.* Urine concentrating ability in infants with sickle cell disease: baseline data from the phase III trial of hydroxyurea (BABY HUG). Pediatr Blood Cancer. 2010 Feb;54(2):265-8.
35. Ataga KI, Orringer EP. Renal abnormalities in sickle cell disease. Am J Hematol. 2000 Apr;63(4):205-11.
36. Kontessis P, Mayopoulou-Symvoulidis D, Symvoulidis A, Kontopoulou-Griva I. Renal involvement in sickle cell-beta thalassemia. Nephron. 1992;61(1):10-5.
37. Maurel S, Stankovic Stojanovic K, Avellino V*, et al.* Prevalence and correlates of metabolic acidosis among patients with homozygous sickle cell disease. Clin J Am Soc Nephrol. 2014 Apr;9(4):648-53.
38. Madu AJ, Okoye AE, Ajuba IC*, et al.* Prevalence and associations of symptomatic renal papillary necrosis in sickle cell anemia patients in South-Eastern Nigeria. Niger J Clin Pract. 2016 Jul-Aug;19(4):471-4.
39. Bolarinwa RA, Akinlade KS, Kuti MA, Olawale OO, Akinola NO. Renal disease in adult Nigerians with sickle cell anemia: a report of prevalence, clinical features and risk factors. Saudi J Kidney Dis Transpl. 2012 Jan;23(1):171-5.
40. Haymann JP, Stankovic K, Levy P*, et al.* Glomerular hyperfiltration in adult sickle cell anemia: a frequent hemolysis associated feature. Clin J Am Soc Nephrol. 2010 May;5(5):756-61.
41. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006 Aug;17(8):2228-35.
42. Audard V, Homs S, Habibi A*, et al.* Acute kidney injury in sickle patients with painful crisis or acute chest syndrome and its relation to pulmonary hypertension. Nephrol Dial Transplant. 2010 Aug;25(8):2524-9.
43. Powars DR, Elliott-Mills DD, Chan L*, et al.* Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med. 1991 Oct 15;115(8):614-20.
44. HAS. Evaluation du rappot albuminurie/créatininurie dans le diagnostic de la maladie rénale chronique chez l'adulte. Haute Autorité de Santé. 2011.
45. McFarlane PA. Testing for albuminuria in 2014. Can J Diabetes. 2014 Oct;38(5):372-5.
46. Alvarez O, Montane B, Lopez G, Wilkinson J, Miller T. Early blood transfusions protect against microalbuminuria in children with sickle cell disease. Pediatr Blood Cancer. 2006 Jul;47(1):71-6.
47. Lebensburger J, Johnson SM, Askenazi DJ*, et al.* Protective role of hemoglobin and fetal hemoglobin in early kidney disease for children with sickle cell anemia. Am J Hematol. 2011 May;86(5):430-2.
48. Fitzhugh CD, Wigfall DR, Ware RE. Enalapril and hydroxyurea therapy for children with sickle nephropathy. Pediatr Blood Cancer. 2005 Dec;45(7):982-5.

49. McKie KT, Hanevold CD, Hernandez C*, et al.* Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J Pediatr Hematol Oncol. 2007 Mar;29(3):140-4.
50. Alvarez O, Miller ST, Wang WC*, et al.* Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. Pediatr Blood Cancer. 2012 Oct;59(4):668-74.
51. Aygun B, Mortier NA, Smeltzer MP*, et al.* Hydroxyurea treatment decreases glomerular hyperfiltration in children with sickle cell anemia. Am J Hematol. 2013 Feb;88(2):116-9.
52. Silva Junior GB, Vieira AP, Couto Bem AX*, et al.* Proteinuria in adults with sickle-cell disease: the role of hydroxycarbamide(hydroxyurea) as a protective agent. Int J Clin Pharm. 2014 Aug;36(4):766-70.
53. Levey AS, Eckardt KU, Tsukamoto Y*, et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005 Jun;67(6):2089-100.
54. Du M, Van Ness S, Gordeuk V*, et al.* Biomarker signatures of sickle cell disease severity. Blood Cells Mol Dis. 2018 Sep;72:1-9.
55. Elsherif L, Pathmasiri W, McRitchie S, Archer DR, Ataga KI. Plasma metabolomics analysis in sickle cell disease patients with albuminuria - an exploratory study. Br J Haematol. 2018 Sep 10.
56. Jerebtsova M, Saraf SL, Lin X*, et al.* Identification of ceruloplasmin as a biomarker of chronic kidney disease in urine of sickle cell disease patients by proteomic analysis. Am J Hematol. 2018 Feb;93(2):E45-E7.