A prospective multicenter trial comparing allogeneic matched related haematopoietic stem cell transplantation after a reduced intensity conditioning regimen, with standard of care in adolescents and adults with severe sickle cell disease
DREPA-RIC

INTERVENTIONAL RESEARCH PROTOCOL
RELATING TO A CELL THERAPY FOR HUMAN USE

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INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

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The research is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

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1 SUMMARY

Full title	A prospective multicenter trial comparing allogeneic matched related haematopoietic stem cell transplantation after a reduced intensity conditioning regimen, with standard of care in adolescents and adults with severe sickle cell disease
Acronym	DREPA-RIC
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Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Although the survival of children with sickle cell disease (SCD) has dramatically improved over the last decades in the US and Europe, mortality remains high in adults. Moreover, many children and most adults develop a chronic debilitating condition due to organ damage. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the unique curative approach; it allows the cure of more than 95% of children transplanted from a matched related donor (MRD) after a myeloablative conditioning regimen[1],[2]. To date, few studies have addressed the role of HSCT in SCD adults, due to the risk of graft versus host disease (GVHD) and to the toxicity expected in older patients with a higher risk of organ damage. The development of safe, non-myeloablative conditioning regimens that allow stable mixed chimerism and avoid GVHD appears as an attractive option for HSCT to cure adults with severe SCD. Four groups have previously reported encouraging results in a total of 81 patients transplanted from matched related mobilized peripheral blood cells after a non-myeloablative conditioning regimen (alemtuzumab and low dose of total body irradiation (TBI)) followed by post-transplant sirolimus. These studies demonstrate a high SCD free survival rate (no death related to transplant, 6 graft failures) and no GVHD. Ninety two percent of these patients were cured with normalized hemoglobin levels, resolution of hemolysis and stable hemoglobin A levels identical to the proportion observed in the donor[3–6]. However, outcome comparison of patients transplanted with patients not transplanted are lacking. We design a prospective multicenter trial targeting patients over 15 years with severe SCD, and compare non-myeloablative transplant (when a matched related donor (MRD) is identified) versus no HSCT (for patients lacking MRD).

Main objective and primary endpoint	The main objective is to assess the benefit of HSCT on the 2-year event free survival calculated from inclusion, compared to standard care. The primary endpoint is the 2-year event free survival. An event is defined as: a) death from any cause b) or an acute grade II-IV GVHD according to the Magic consortium 2016 (Appendix 20.3) or a moderate or severe chronic GVHD according to the NIH classification, c) or 3 hospitalizations for VOC defined according to usual criteria d) or one ACS defined by usual clinical criteria and a pulmonary infiltrate on chest film and/or thoracic computed-tomography (CT) scan e) or a stroke defined as a clinical event confirmed by an MRI or a cerebral or cervical stenosis > 25% in a new territory, evaluated by MRI and MRA or apparition of a silent infarct f) or increased of at least +10% of tricuspid regurgitation velocity, (confirmed by 2 echocardiographies performed with a delay of at least 3 months) compared with pre-inclusion value for patients with TRV ≥ 2.7 at inclusion We hypothesize that the 2-year event free survival will be of 80% after HSCT versus 40% in the no-transplant group.
Secondary objectives and endpoints	**The secondary objectives:** Compare in the both groups at 2 years: • Overall survival • Total days requiring hospitalization after the first 5 months post-inclusion. • Acute complications of SCD: VOC, ACS, priapism • Stroke, silent infarct, cerebral or cervical stenosis on MRA/MRI • Hemolytic index, hematologic and biochemical parameters • Organ function (kidney, eyes, heart, lung, liver, bone) • Grade III-IV Infectious complications • Need for transfusion from 6 months post-inclusion • Alloimmunization rate • Iron overload • Chronic used of oral opioids • Nutritional involvement • Gonadic function and fertility • Quality of life, anxiety and depression • Cost To evaluate in the transplant group: chimerism, engraftment, GVHD, patients free of sirolimus at 1 and 2 year post-transplant **The secondary end points:** • Death • Number of days requiring hospitalization with exclusion of the 5 first months post-inclusion • Clinical adverse events: number of VOC and ACS requiring hospitalization, number of hospitalization in intensive care unit • Number of priapism • Number of stroke

	• Changes in biological parameters: LDH, aminotransferase, gamma-GT, alkaline phosphatase, bilirubin, PR, APTT, hemoglobin level, hematocrit, mean corpuscular volume, percentage of hemoglobin variants, reticulocyte, white blood cells and platelets counts, estimated glomerular function rate • Microalbuminuria/creatininuria ratio • Ferritin and transferrin saturation level • Gonadic function: Spermogram in men, LH, FSH, oestrogen in women, testosterone in men at M24; Number of amenorrhea in women. Number of parity • Eye function • Heart (pulmonary hypertension, auricular or ventricular dilatation, left ventricular mass and function) by a transthoracic echocardiography. • Lung function (pulmonary function tests, 6 min walk test) • Bone function: new episode of avascular osteonecrosis and of fracture • Central nervous system function: (with MRA/MRI) • Liver and heart magnetic resonance imaging for iron overload evaluation in patients with ferritin >1000 microg/L at the inclusion, M12 and M24 • Number of red blood cell packed transfused from 6 months post-inclusion • Number of delayed hemolytic transfusion reaction (DHTR) • Oral opioid consumption • Quality of life questionnaire (MOS SF36) • Hospital Anxiety and Depression Scale (HADS) questionnaire • Change in weight • Severe infections (CTAE score: grade 3-4) • GvHD incidence and grading in HSCT patients • Chimerism in HSCT assessed on total blood population and T lymphocyte subset • Cost: evaluated by the days of hospitalization from the inclusion
Design of the study	Quasi experimental design: phase 3, prospective controlled multicenter, cohort study with 2 groups of patients defined by genetic randomization. Once the eligibility criteria and the informed consent have been obtained, HLA typing will be performed to identify potential HLA MRD and define 2 groups: • group 1 “exposed” patients: if an HLA identical sibling is identified, patients will receive HSCT • group 2 “unexposed patients”: patients lacking an HLA identical sibling will received the best standard care **Transplant arm:** - Red-cell exchange will be performed to reduce hemoglobin S levels to 30% or less during the 3 months preceding transplant

	- The conditioning regimen will consist in 300cGY TBI at D-2 and alemtuzumab IV (Total dose: 1mg/kg) for 5 days (D-7 to D-3) - The stem cell source will be G-CSF mobilized peripheral blood stem cells; CD34 target dose is 10 x 10^6 or more per Kg body weight. - GVHD prophylaxis will consist in sirolimus for during 1 year, then sirolimus will be tapered and stopped at 15 months post-transplant. **No transplant arm**: patients will receive the best standard care according to their situation and their previous treatment: initiation of Hydroxyurea, continuation or optimization of the dose of Hydroxyurea, initiation or continuation of transfusion program (TP), initiation of a new drug proved to improve SCD and having authorization to use in France.
Population of study participants	Adolescents and young adults (15-45 years)
Inclusion criteria of patients	• SCD patients (SS/Sβ0) • Aged:15 to 45 years • With at least one non-SCD sibling > 16 years from the same parental couple • Who presented at least one of the following criteria: - 2 VOC requiring hospitalization over the last 2 years - At least 1 severe ACS within the past 2 years defined as followed: ACS requiring red cell transfusion, or hospitalization in intensive care unit, or ACS with PaO2 < 60mmHg or arterial blood PH < 7.35 or PaC02 > 50mmHg or need more than 4 liters of 02/ mn for reaching Sat02 > 98% - 1 VOC requiring hospitalization over the last 2 years and history of recurrent ACS (three or more) - History of ischemic stroke or cerebral/cervical arterial stenosis ≥ 25% or apparition of silent infarct in the last 2 years - Pulmonary hypertension defined by mean pulmonary artery pressure ≥ 25 mmHg at rest, determined by right heart catherization - Osteonecrosis of at least 2 joints including one diagnosed in the past 2 years. - Sickle nephropathy (estimated glomerular filtration rate (by CKD EPI formula) <100 ml/min/1.73M2 and persistant microalbuminuria (microalbuminuria/creatininuria ratio >10 mg/mmol) without other cause of nephropathy) • Requiring treatment with Hydroxyurea or chronic transfusion, or already treated by Hydroxyurea or transfusion program (TP) at inclusion. • For : Patients already receiving chronic transfusions for VOC or ACS not responding to hydroxyurea : they will be eligible, if they provided before the beginning of chronic transfusions at least : - 2 VOC requiring hospitalization over the last 2 years - At least 1 severe ACS within the past 2 years defined as followed: ACS requiring red cell transfusion, or hospitalization in intensive care unit, or ACS with PaC02 < 60mmHg or arterial blood pH < 7.35 or PaC02

	> 50mmHg or need more than 4 liters of O2/mn for reaching Sat02 > 98% - 1 VOC requiring hospitalization over the last 2 years and history of recurrent ACS (three or more) • Contraception during all the study period by sirolimus for women of child bearing potential • Signed informed consent • Amenable to HLA typing, HSCT if an HLA-identical sibling is available. • Patients affiliated to the French health care insurance
Inclusion criteria of donors	• Age: 16 to 60 years • Hb electrophoresis: AA, AS or AC • Donor with usual clinical and biological eligibility criteria for G-CSF mobilization and peripheral blood stem cell bone collection including legal viral serologies assessment authorizing the transplant • Being HLA identical with the patient • Negative Covid-19 test at time of HSCT mobilization In patient with several potential donors (several matched sibling donor), ABO matched donor will be chosen in priority.
Exclusion criteria of patients	• Performance status: ECOG scale>1 • Pulmonary function: FEV1 et FVC < 50% of the theorical value • Post capillary and severe pre-capillary pulmonary hypertension with measured mean pulmonary artery pressure at rest >35 mmHg • Cardiac ejection fraction ≤ 45% • Estimated glomerular fraction rate (GFR) <50ml/mn /1.73m^2 • Conjugate bilirubin >50 µmole/L, cirrhosis, ALAT>4N • Severe uncontrolled infection • Known hypersensitivity of alemtuzumab • Known hypersensitivity to murin proteins and to the following excipients: disodium edetate, polysorbate 80, potassium chloride, potassium phosphate monobasic, sodium chloride, dibasic sodium phosphate, water for injections • Positivity for HIV • Pregnancy or breast-feeding women • Alloimmunization or Delayed Hemolytic Transfusion Reaction precluding red cell transfusions • Previous solid organ transplant or hematopoietic stem cell transplant. • Uncontrolled hypertension • History of arterial dissection of the cervicocephalic arteries • History of angina pectoris or myocardial infarction
Interventions or product under investigation	Patients should be transplanted within 1 to 6 months of inclusion. *HLA* Matched related HSCT a) Red-cell exchange will be performed to reduce hemoglobin S levels to 30% or less during the 3 months preceding transplant

	b) Consider fertility preservation techniques according patient's age, pregnancy wish and evaluation of ovarian function c) The conditioning regimen will consist in 300cGY TBI at D-2 and alemtuzumab IV (Total dose: 1mg/kg) for 5 days (D-7 to D-3) d) The stem cell source will be G-CSF mobilized peripheral blood stem cells. CD34 target dose is 10 x 10^6 or more per Kg body weight. If the number of CD34 cells is not obtained after one leukapheresis, a second will be planned the next day to reach the goal. a) GVHD prophylaxis with consisted in sirolimus for 1 year, then sirolimus will be tapered and stopped at 15 months post-transplant.
Comparator arm	Patients will receive the best standard care according to their situation and their previous treatment: initiation of Hydroxyurea, continuation or optimization of the dose of Hydroxyurea, initiation or continuation of TP, initiation of a new drug proved to improve SCD and having authorization to use in France.
Other interventions added by the study	HSCT
Expected benefits for the participants and for society	In the transplant arm, the benefit expected is the cure of the disease, i.e. absence of post-transplant new complications related to SCD.
Risks added by the study	In the no transplant arm, the risks are the complications of the disease despite supportive care including hydroxyurea and transfusions programs. Chronic transfusions can lead iron overload and alloimmunization. Hydroxyurea can lead hypofertility. In this arm: consultation every 3 months until M24. In the transplant arm: Hospitalization for 4 to 6 weeks followed by weekly consultations during the 3 first months post-transplant, then 1 monthly consultation from 3-6 months and consultation every 3 months until M24. Some of the most common toxicities associated with the transplantation (including the reduced conditioning regimen and GVHD prophylaxis) are: - Graft versus host disease according to the Magic consortium 2016 (Appendix 20.3) criteria - Chronic GVHD according to the NIH classification - Infection - Fever, aplasia, pancytopenia, neutropenia, thrombopenia, anemia - Gastrointestinal: nausea, vomiting - Cardiovascular: arterial hypertension - Neurological disorders: visual disorders - Miscellaneous: serum sickness (skin rashes, pain and swelling of the joints) and anaphylaxis (hypotension, difficulty breathing and severe hives, mucositis) Transplant may potentially lead transplant related mortality and graft versus host disease, but no case was observed in the first 81 cases reported in the literature. The risk of long term complications as infertility remains to be evaluated in this setting of RIC transplant.

Scope of the study	Hematology/Haemovigilance and therapeutic transfusion
Number of participants included	78 patients
Number of valued sites	**37** centres: **22** recruiting centres and **15** transplant centres (some recruiting site, also transplant patients)
Schedule for the study	State: - inclusion period: **3 years** - participation period (treatment+follow-up): **2 years** - total duration of the study: **5 years**
Number of enrolments expected per site and per month	2 patients expected per recruiting site per year
Statistical analysis	A single efficacy analysis is planned: EFS will be compared between two groups using log-rank test, and the effect of HSCT assessed by Hazard Ratio using a Cox model. The primary endpoint is event free survival at 2 years calculated from inclusion. Event will be defined as followed: a) death from any cause b) or an acute grade II-IV GVHD according to the Magic consortium 2016 (Appendix 20.3) or a moderate or severe chronic GVHD according to the NIH classification, c) or 3 hospitalizations for VOC defined according to usual criteria d) or one ACS defined by usual clinical criteria and a pulmonary infiltrate on chest film and/or thoracic computed-tomography (CT) scan e) or a stroke defined as a clinical event confirmed by an MRI f) or a cerebral or cervical stenosis > 25% in a new territory, evaluated by MRI and MRA g) or increased of at least +10% of tricuspid regurgitation velocity, (confirmed by 2 echocardiographies performed with a delay of at least 3 months) compared with pre-inclusion value for patients with TRV $\geq$ 2.7 at inclusion h) or apparition of a silent infarct or a cerebral/cervical stenosis >25% in a new territory, or increase >25% of previous stenosis evaluated MRI and MRA Event free survival at 2 years calculated from inclusion will also be described in the HSCT group. Overall survival will be defined as the time between date of inclusion and death due to any cause or to date of last follow-up. A propensity score matching analysis will be also performed as a sensitivity analysis to handle potential residual imbalances between arms in confounders. A sequential analysis of tolerance data will be performed, using Bayesian methods. We hypothesize that the 2-year event free survival will be of 80% after HSCT versus 40% in the no-transplant group.
Sources of monetary support	*French Ministry of Health, PHRC N-2017*
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 Context

2.1.1 Current management of sickle cell disease

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide, resulting from a single-nucleotide substitution, leading to a propensity toward hemoglobin polymerization and sickling of red blood cells. Sickle cell disease is characterized by anemia, ongoing hemolysis, and acute and chronic vaso-occlusive complications affecting multiple organs. SCD affects over 100,000 Americans and approximately, 26,000 patients in France, half of them being adults and living in Ile-de-France area[7]. The frequency of the disease worldwide is uncertain and is likely to be underestimated in Asia and Africa. SCD kills nearly half a million people annually.

During the last decades, survival has been improved, due to a) use of prophylactic penicillin, and vaccinations against *streptococcus pneumoniae* and *haemophilus influenzae*, b) the implementation of newborn screening, c) the use of hydroxyurea and program of chronic red blood cells (RBC) transfusion therapy, d) iron chelation and e) transcranial doppler screening to identify children at increased risk of stroke[8–14].

Long-term hydroxyurea usage (oral route every day), has been shown to alter the natural history of SCD in peer-reviewed studies. In two randomized, placebo-controlled studies, hydroxyurea was shown to decrease the frequency of VOC, ACS, RBC transfusion and hospitalization rates in both adults and children with sickle cell anemia[15,16].

Program of chronic transfusion therapy is a very effective treatment of severe SCD patients in the short/medium term. It dramatically reduces the risk of stroke in children with high velocities in transcranial doppler[13,14] and number of VOC and ACS requiring hospitalizations in patients who presented these complications despite hydroxyurea therapy. Even when extensively matched, red blood cell transfusion can lead to red cell or HLA allo-antibodies[17] and life threatening delayed hemolytic transfusion reaction, an emerging problem in adults with SCD[18]. Moreover, most of these chronically transfused patients also develop iron overload, and serious problems of venous access. The impact of chronic transfusion on school activity or work as well as the quality of life of patients treated with chronic transfusion has to be adequately assessed.

2.1.2 Prognosis of sickle cell disease

Due to the remarkable therapeutic advances in the management of SCD in the last decades, more than 95% of children with SCD in developed countries, survive to adulthood[19,20]. However, transition in care from the pediatric to the adults medical setting often results in loss of follow-up and increased risk of morbidity and mortality[21]. Moreover, most adults develop a chronic debilitating condition due to the chronic effects of sustained haemolytic anemia and vaso-occlusive events driving the development of end-organ complications and leading early death. In US over 30% of adults with SCD were on disability and over 50% were unemployed[22]. Quality of life is severely impacted by chronic pain, narcotic dependence, stroke, renal failure, thrombosis, pulmonary hypertension, blindness, priapism, psychologic disturbance and infections episodes.

Age of death and survival in SCD adults leaving in industrialized countries:

In a population of 16,654 American SCD-related deaths reported between 1979 and 2005 (before a large use of hydroxyurea), the mean age at death was 33.4 years for males and 36.9

years for females. This report confirmed the significant decrease in mortality for children with SCD, but highlighted the increase of mortality for adults.[23]

Several studies have shown a positive impact of hydroxyurea on SCD adult survival. In the longest observational US prospective study following SCD adults during 17.7 years (ended in August 2009), the annual mortality rate of 4.4% person-years and patients exposed to long-term hydroxyurea displayed reduced mortality.[24] In a population of 330 Greek SCD adults mostly HbS-β^+ and HbS-β^0 thalassemia, patients who received hydroxyurea, based on the severity of the SCD symptoms, had a significantly reduced mortality in comparison with patients not exposed to hydroxyurea: 10-year mortality of 14% versus 35%.[25] In the opposite, several studies did not find an advantage of survival in patients treated by hydroxyurea: in the first including 534 american SCD adults the mortality rate was of 25% after a 10-year follow-up with no impact of hydroxyurea;[26] in the prospective walk-PHaSST cohort, enrolling 632 US or UK patients (median age 37 years), the mortality rate was 3.8% for the SS patients, with no difference between hydroxyurea users or not**,** but the median follow-up was short (only 29 months).[27]

The table 1 summarizes data of survival in SCD patients, in large series conducting after the approval of hydroxyurea. These series included not only HbSS, $HbSB^0$ but also HbSC and $HbSB^+$ genotypes of SCD. The median age at death of deceased subjects varied from 36.6 to 53 years, according to the reports. As expected, the prognosis was poorer in patients with HbSS, $HbSB^0$ compared those with HbSC and $HbSB^+$ SCD[26–32].

Publication	Nb of patients	Disease genotypes	Median/mean age at death in deceased patients	Duration of follow-up
Cabrita *et al*, 2013 UK	164	HbSS, HbS b^0,HbSC, HbSb+, HbSD	49 (range 25-82)	68 months (IQR:48-68)
Elmariah *et al* , 2014 USA	542	HbSS, HbS b^0,HbSC, HbSb+	45 (range 20-86)	9.3 years (range: 2.7-10.5)
Gladwin *et al* , 2014 USA	605	HbSS, HbSC	41 (range 21-65)	2.4 years (range: 0.04-3.4)
Schimmel *et al* , 2015 Netherlands	85	HbSS, HbS b^0,HbSC, HbSb+	53 (IQR: 37-60)	82months (IQR:75-85)
Karacaoglu *et al* , 2016 Turkey	656	HbSS, HbS b^0	36.6 ± 13	66 ± 44 months
Maitra *et al* , 2017 USA	161	HbSS, HbS b^0,HbSC, HbSb+, HbSD	48 (range 30-70)	6.4 years (range:0.06-10.3)
Fitzhugh *et al*, 2010 USA	240	HbSS, HbS b^0,HbSC, HbSb+	39 (range 21 – 83)	5 years

In France, the median age at death of 36 years for SCD patients, (including children and adults), did not change between the two studied periods: 2001-2005 and 2006-2010 (report of the French health ministry *"l'état de santé de la population en France 2015 »).*

Âge moyen et âge médian au décès liés à la drépanocytose selon la période pour la France métropolitaine et les DOM

	France métropolitaine			DOM		
Paramètres	2001-2005	2006-2010	Total	2001-2005	2006-2010	Total
Nombre de décès	118	134	252	88	93	181
Âge moyen	34,8	33,4	34,0	39,9	41,9	41,0
Age médian	32,0	33,5	33,0	41,5	44,0	42,0

Source • Inserm-CépiDc. Exploitation : InVS.

In the monocentric cohort study of 656 adults SCD patients followed in the referral center of Creteil, France, the 48-month mortality was 7.6%. Interestingly, Gardner et al, recently showed, in a cohort of patients followed at a single center in the United Kingdom, that in carefully controlled situations such as structured comprehensive clinics that include transitioning of care of the older adolescent from a pediatric to an adult setting, the median survival for adults is 67 years, but structured comprehensive clinics are not the norm.[33]

Finally, it's important to stress the point that mortality rates evaluated in the cohorts of patients are probably underestimated since many patients were lost to follow-up, due in some to outpatient death.

Risk factors of death in adult SCD patients

In patients with SCD, death was mostly secondary to acute episodes of pain, ACS or stroke. In the historical series reported by Platt et *al.*, ACS, renal failure, seizures, high white blood cell count (WBC) and low level of fetal hemoglobin (HbF) were associated with an increased risk of early death in HbSS patients.[34] More recent studies, conducted after approval of hydroxyurea, show an increased risk of death in patients with higher age, male gender, elevated echocardiography-derived tricuspid regurgitant jet velocity (TRV), pulmonary hypertension[35–38], elevated levels of N-terminal probrain natriuretic peptide (NT-pro-BNP),[39] history of asthma and/or wheezing,[40] end-stage renal disease requiring dialysis, severity of hemolysis,[41–43] and prolongation of QTc interval, elevated LDH value , high bilirubin ferritin values, low hemoglobin rate, high platelets and reticulocyte counts. [44] As reported in first by Gladwin et *al*., a peak TRV equal to or greater than 2.5 m/second was found to be strongly associated with an increased risk for death in SCD. (rate ratio, 10.1; 95 percent confidence interval, 2.2 to 47.0; P<0.001); thus, in the 32 percent of adult patients with TRV > 2.5 m/sec, followed for a median time of 18 months, the survival drop to 85% at 20 months, compared to more than 95% in other patients.[35] However, other reports show that adults with elevated TRV assessed by doppler echocardiographic who are found not to have pulmonary hypertension at right catheterization have similar survival to SCD patients without elevated TRV.[37,45,46] In a series of 55 patients with pulmonary hypertension confirmed by right catheterization, the estimated median survival time was 6.8 years after ascertainment of pulmonary hypertension.[45] The right heart catheterization remains the gold standard exam for diagnosis of pulmonary hypertension, and is recommended by the French guidelines, in patients with TRV>2.8m/s.[47] Reports suggest that exchange blood transfusion, is beneficial to SCD patients with pulmonary hypertension,[48] but randomized, controlled trials of exchange transfusion are needed to evaluate long-term outcome of these patients. N-terminal pro–brain natriuretic peptide (NT-proBNP) > 160 pg/Ml was also associated with increased mortality. [27] In the walk-PHaSST (Sildenafil Therapy for Pulmonary Hypertension and Sickle Cell Disease) trial, subjects with a TRV >3m/s had a 2-year mortality rate of 12%.[49]

2.1.3 HLA matched related HSCT in children with SCD: indications and results

To date, allogeneic hematopoietic stem cell transplant (HSCT) is the only curative therapy, but access is limited for several reasons, including donor availability, socio-cultural and economic barriers.[50] Yet, far less than 1% of the SCD population in the United States has received a transplant. A key barrier is a prevailing assumption that HSCT is risky and carries a mortality rate that exceeds mortality experienced with a supportive care approach. In addition, there are risks of infertility and of graft-versus-host disease (GVHD), which can cause a chronic debilitating disorder. Thus, SCD patients and transplant physicians alike debate the burden of morbidity from a chronic disease and mortality from the disease, versus the curative option with transplantation and the risk of transplant-related complications and mortality. In addition, risks of transplantation should be compared to the risks of long-term use of conventional treatments, hydroxyurea (risk of infertility or micellaneous adverse events) and transfusion (alloimmunization, iron overload) and the natural history of patients treated with this drug : 14% mortality at 10-years in patients taking hydroxyurea[25]or 3.8% at 2.5 years[27] as detailed above.

The first experience of HSCT in SCD was reported in 1984 by Johnson et *al.* in a child with both acute leukemia and SCD. It was followed by several reports of myeloablative allogeneic BMT from matched sibling donors in children. These data firmly established that SCD is a potentially curative disease following myeloablative allogeneic BMT from a healthy HLA matched sibling donor. The table below (*Talano, European Journal of Haematology 2014*)

depicted the experience of the principal groups in myeloablative HLA-identical sibling transplant for SCD in children.[1,51–56]

Table 1 HLA-matched sibling AlloHSCTs after myeloablative conditioning in patients with SCD

Author	Country or registry	*n*	OS (%)	EFS (%)	Graft rejection (%)	AGVHD (%)	CGVHD (%)
Panepinto (3)	CIBMTR	67	97	85	15	10	22
Walters (2)	USA	22	91	73	18	1	1
Bernaudin (4)	France	87	93	86	7	13	20
Locatelli (5)	Eurocord, Oakland	160	97	92	N/A	N/A	N/A
Dedeken (6)	Belgium	50	94.1	85.6	8	10	20
Maheshwari (7)	USA	16	100	100	0	13	0
Lucarelli (8)	Nigeria Albania, Kuwait, Iraq, Lebanon	40	91	91	0	17.5	5

Additionally, Walters et *al.* has recently combined, results of 218 children transplanted from a HLA-identical sibling donor after a myeloablative regimen; 208 (95%) survived after transplantation and 200 (92%) survived free of SCD. At last follow-up only 6 survivors (3%) were receiving immunosuppressive therapy to treat chronic GVHD. [50] A 15% to 20% GVHD rate with cyclosporine-based post-graft immunosuppression in the myeloablative setting has been reported.

Similar results have been even more recently reported by Gluckman et *al.* in 1000 recipients of HLA-identical sibling transplants performed between 1986 and 2013 and reported to the European Blood and Marrow Transplant, Eurocord and the Center for International Blood and Marrow Transplant Research.[2] In this cohort, mostly pediatric (85% of patients < 16 years), the 5-year event-free and overall survival was 91.4% (95% CI 89.6%-93.3%) and 92.9% (95% CI 91.1%-94.6%), respectively. Event-free survival was lower with increasing age at transplantation (hazard ratio [HR] 1.09; p<0.001) and higher for transplantations performed after 2006 (HR 0.95, p=0.013). Twenty-three patients experienced graft failure. Incidence of chronic GVHD was 14.3% (95% CI 12%-16.9%), lower in children (< 16 years). In a recent prospective study comparing matched related transplant versus chronic transfusions in children with abnormal cerebral velocity, Bernaudin et *al.* shown that HSCT decreases velocities in more patients than chronic transfusions without toxicity. Thirty-two patients with a matched related donor were transplanted; all of them successfully engrafted; 3 presented acute-GvHD grade≥II, but no chronic-GVHD were observed. All patients were alive at 1 year (Bernaudin Submitted to JAMA).

Considering the results of related HLA-identical transplant in SCD children, it's interesting to stress the point that the 2-year transplant-related mortality risk after HLA-identical sibling donor transplantation appears very similar to the risk in children with SCD who receive standard supportive care. This notion is further strengthened by a recent report that described a cohort of 469 children and adults with SCD in Belgium in which the 15-year survival rate after transplantation compared with supportive care was not significantly different, although survival was superior in a group treated by HSCT.[57] Historically, indications for HSCT in SCD children were often restricted to those with a clinical stroke or recurrent vaso-occlusive complications such as pain and/or acute chest syndrome despite receiving optimal supportive care. More recently, indications in children also include other complications as suggested by recommendations from Walters et*al.* on the table below (*Table from Angelucci, Haematologica 2014).*

Table 3. Indication for allogeneic HSCT suggested by Walters *et al.*

Stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
Impaired neuropsychological function with abnormal cerebral MRI scan
Stage I or II sickle lung disease
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
Bilateral proliferative retinopathy with major visual impairment in at least one eye
Osteonecrosis of multiple joints
Red-cell alloimmunization during long-term transfusion therapy

However, as the survival rates in transplant and nontransplant cohorts converge, referring SCD children for HSCT solely after significant or irreversible complications in is no longer appropriate. Accordingly, in 2014 an international expert panel on behalf of the EBMT Inborn Error and EBMT Pediatric Working Parties, recommended transplantation as early as possible, preferably at preschool age, for young patients with symptomatic SCD and an HLA-identical sibling donor .[58]
Myeloablaltive conditioning regimen was mostly based on busulfan (14-16 mg/kg) associated with high dose cyclophosphamide or more recently fludarabine.[50]*In vivo* T cell depletion by Antithymocyte globulin (ATG) has been shown to reduce graft failure from 23% to 3%, as reported by Bernaudin et *al.*[1,50,59] Other groups has used alemtuzumab for *in vivo* T cell depletion. Unmanipulated bone marrow or cord blood (when available), from HLA identical related donor are the stem cell source recommended. What is remarkable is that despite myeloablative dosing in the conditioning regimens, a mixture of both donor and recipient hematopoietic cells, termed mixed donor chimerism, is consistently observed in approximately 10% to 20% of these children.[1,50,59] Interestingly, this mixed chimeric state with the presence of both recipient and donor blood cells, is sufficient to direct bone marrow to preferentially produce donor-type hemoglobin (rather than abnormal SS hemoglobin of the recipient), and red cells revert the SCD phenotype, and minimize the risk of GVHD. Thus, the absence of full donor engraftment, reflected by mixed chimerism is usually associated with lower incidence of GVHD. This observation has both confirmed the therapeutic efficacy and secured the goal of mixed chimerism for the hemoglobinopathies.

2.1.4 HLA matched related HSCT in adults with SCD

2.1.4.1 Indications

To date, few studies have addressed the role of HSCT in SCD adults, due to the potential risk of graft-versus-host disease and to the high toxicity expected in patients with organ damage. However, the transplant experience is growing in adults with SCD. At time, there is no general agreement on referral of patients with SCD to an HSCT program. The decision can depend on factors including patient age, complications of SCD, existence of severe comorbidities, and sociocultural setting. There is a potential for a wider acceptability of common indications have included cerebrovascular disease, recurrent VOC and ACS despite hydroxyurea, osteonecrosis and red cell alloimmunization.[3,60] The indications for BMT will continue to evolve as the availability of alternative donors, engraftment rates, and safety of BMT increases, including use of non-myeloablative conditioning regimen. The table below summarizes the indications of HLA matched related HSCT in adults with SCD in trials or according to recommendations from different groups.

Indications of HLA matched related HSCT in adults with SCD

Publications or trial	Indications
Gluckman, blood 2013	Stroke, Elevated TCD velocity , Recurrent ACS, Recurrent splenic sequestration, Recurrent VOC Silent stroke with cognitive impairment, Pulmonary hypertension, Pulmonary hypertension, Osteonecrosis, Sickle nephropathy, RBC alloimmunization, Recurent priapism
Walters, BBMT 2016	Clinically significant neurologic event (stroke) or any neurologic deficit lasting >24 hr History of 2 or more episodes of ACS in the 2-yr period preceding HSCT despite the institution of supportive care measures (ie, asthma therapy and/or HC) History of 3 or more severe pain crises per year in the 2-yr period preceding enrollment despite the institution of supportive caremeasures (ie, treatment with hydroxyurea) Administration of regular RBC transfusion therapy, ≥ 8 or more transfusions per year for 1 yr to prevent vasoocclusive clinical complications (ie, pain, stroke, and acute chest syndrome) An echocardiographic finding of tricuspid valve regurgitant ≥jet 2.7 m/s
NIH indications	Irreversible end-organ damage
Hsieh Blood 2011	Stroke or clinically significant CNS event Elevated TRV ⩾2.6 m/s Sickle-related renal insufficiency (Cr ⩾ 1.5 times the upper limit of normal or biopsy proven), Sickle hepatopathy (including iron overload), Reversible sickle complication not ameliorated by hydroxyurea, Two or more VOC requiring hospitalizations for several years, Any ACS while on hydroxyurea
STRIDE trial	Clinically significant neurological event or any neurological deficit lasting ⩾24 h TRV ⩾2.7 m/s ⩾ 3 severe VOC pain episodes per year in the past 3 years despite supportive care ⩾ 2 episodes of ACS with a history of recurrent hospitalizations or exchange transfusions in the past 2 years despite supportive care Receives regular RBC transfusion therapy, defined as ⩾ 8 per year for 1 year or longer Patients must have symptoms despite supportive care such as hydroxyurea
Adetola Hematol Oncol Stem Cell Therapy 2017	SCD unresponsive to hydroxyurea therapy with - Overt stroke or central nervous system event lasting >24 h - Impaired neuropsychological function with abnormal cerebral magnetic resonance imaging and angiography - Elevated TCD velocity unresponsive to hydroxyurea or chronic blood transfusion therapy - Recurrent acute chest syndrome despite hydroxyurea therapy - Recurrent severe pain episodes despite hydroxyurea therapy - Red cell alloimmunization plus established indication for chronic blood transfusion therapy - Pulmonary hypertension or an echocardiographic finding of tricuspid valve regurgitant jet velocity ⩾ 2.7 m/s - Recurrent priapism - Sickle nephropathy - Bone and joint involvement - Sickle retinopathy - Stage I or II sickle lung disease

ACS: acute chest syndrome; NIH, National Institutes of Health; MRI, magnetic resonance imaging; TCD, transcranial Doppler; TRV, tricuspid regurgitant velocity; VOC, vaso-occlusive crises.

2.1.4.2 Results

a) Myeloablative conditioning regimen

The possibility of successful myeloablative HSCT in young adults was suggested by a report from of 15 patients older than 16 years of age who have received a HLA matched related transplant after a full-dose conditioning regimen.(61) All the patients received the same BU-CY-ATG regimen and a GVHD prophylaxis based on methotrexate and cyclosporine, as reported in children. Only 1 death was observed in a patient with severe cerebral vasculopathy and Moya-Moya who suffered of massive cerebral hemorrhage at day 32 post-transplant. Only 2 patients experienced moderate chronic-GVHD. With a median follow-up of 3.4 years (range 1-16.1), overall disease-free survival was 93.3% ± 0.12. All survivors currently enjoy a normal quality of life without immunosuppression. Chimerism at 1 year was full-donor in 12 patients and mixed but > 75% donor in 2 patients. Although limited, this experience demonstrated that full myeloablative transplantation has an acceptable toxicity in selected young adults with SCD. In fact, the authors did not report any unusual complications because of pre-transplant organ damage, such as veno-occlusive disease or renal failure.
Updates on the results of HLA-matched sibling HSCT for SCD performed world-wide between 1986 and 2013, were recently reported to the European Blood and Marrow Transplant,

Eurocord, and the Center for International Blood and Marrow Transplant Research (CIBMTR) by Gluckman et *al*. From the 1000 patients included in the study, 154 were over 16 years old (median age: 19.3 years (range 16.0-54.4). Most adult patients (73.4%) received a myeloablative conditioning regimen. The 5-year overall survival and disease-free survival were 81% for patients aged >16 years. The 5-year probability of GVHD-free survival was 77% for patients aged >16 years and the graft rejection rate was 2.3%.[(2)]

b) Reduced intensity conditioning regimen

Non-myeloablative conditioning regimens have several theoretical advantages over myeloablative regimens in patients with SCD. First, patients with SCD, especially adults, often have significant end-organ damage (renal, pulmonary, liver, etc.). Non-myeloablative regimens are less toxic; thus, children and adults with mild to moderate end organ toxicity would still be eligible for HSCT. Moreover, most non-myeloablative regimens allows less gonadal failure. However, a potential drawback off non-myeloablative conditioning is a higher rate of graft failure and mixed chimerism. In this setting, stable mixed chimerism is accepted as it usually spares the red cell compartment, mostly replaced by normal donor red cells, allowing resolution of SCD symptoms.
In 2004, Jacobsohn et *al.* reported 13 pediatric patients with non-malignant disorders who underwent a HSCT after reduced intensity conditioning regimen. Most patients transplanted for hemoglobinopathies rejected the graft.[(62)] Horwitz et *al.* reported the outcome of two adult patients (age 21 and 27 years, respectively) with SCD (one with end-stage renal disease) that received a fludarabine-based non-myeloablative BMT from HLA-matched sibling donors.[(63)] Both patients achieved full donor erythroid chimerism with normal blood counts and could discontinue immunosuppression.
The table below summarizes the principal experiences of reduced intensity transplants from related matched donor in children and adults with SCD

Study	n	Regimen	GvHD prophylaxis	Survival (%)	Graft rejection (%)	GvHD(%) acute/chronic	EFS (%)
Van Besien, *BMT 2000*	2	HDM, Flu, ATG	Tacrolimus, + MTX	0	0	100/50	0
Iannone BBMT 2003	6	2 Gy TBI, Flu	Tacrolimus or CSA +MMF	100	100	16/0	0
Jacobsohn *Lancet 2004*	1	Bu:6.4 mg/kg, Flu, ATG	CSA+MMF	0	100	100/100	0
Horan BMT 2005	3	2 Gy TBI, Flu, ATG	CSA+MMF	100	0	0	100
Horwitz *BBMT 2007*	2	2 Gy TBI, Flu, CY, alemtuzumab	MMF	100	0	0	100
Krishnamurti BBMT 2008	7	Bu:6.4 mg/kg, Flu, ATG, TLI 5 Gy	CSA+MMF	100	14	14/14	86
Matthes *Eur J Haem 2013*	8	HDM, Flu, Thiotepa, or TLI, ATG or alemtuzumab	CSA+MMF	0	0	0	100
Hsieh JAMA 2014	30	3 Gy TBI, alemtuzumab	Sirolimus	97	13	0	87
King *AJH 2015*	43	HDM, Fluda, alemtuzumab	CSA+ MTX or MMF	93	2	23/13	90
Saraf BBMT 2015	13	3 Gy TBI, alemtuzumab	Sirolimus	100	7	0	93
Ozdogu BMT 2018	20	CY,Flu, BU2, ATG, 2Gy TBI	Sirolimus high CY	100	0	Gr II-IV/5%/0	100
Guilcher *ASH 2017*	14	3 Gy TBI, alemtuzumab	Sirolimus	100	0	0	100
Alzahrani *EBMT 2018*	24	3 Gy TBI, alemtuzumab	Sirolimus	100	0	0	100

EFS: event free survival, HDM: high dose melphalan, Flu: fludarabine, MTX: methotrexate, MMF: mycophenolate, TBI: total body irradiation, TLI: total lymphoïde irradiation, CSA: cyclosporine A, BU: busulfan

Different conditioning regimen were used, all including ATG or alemtuzumab and most including fludarabine, with decreased dose of alkylant (Busulfan or Melphalan) or total body irradiation (TBI) as compared with the dose used in the myeloablative conditioning regimen. Stem cell source were bone marrow, peripheral blood stem cell (PBSC) or cord blood. Event free survival varied from 50% to 100% according to the studies.[3,4,64–67]
The NIH group developed a very interesting approach based on myelosuppression with tolerance induction, using a conditioning regimen associating a low dose of TBI with alemtuzumab and a post-transplant immunosuppression by sirolimus, with the aim to induce a long-term tolerance. This approach, which was chosen in the present study, is detailed in the paragraph ".2.2 Existing knowledge relating to the condition under investigation"

2.1.5 Long term outcomes after HSCT

A major issue after myeloablative HSCT is the related conditioning late effects and the improvement of SCD related complications. An important benefit of successful HSCT is the elimination of sickle erythropoiesis, thereby significantly reducing the risk of sickle related complications [1,4,68].
Long-term result analysis performed by Bernaudin et al showed a long-term hematological reconstitution with mostly full donor chimerism or stable mixed chimerism.[1] Quality of life

was markedly improved. In the majority of cases, it was possible to interrupt immunosuppression between 6 and 9 months after HSCT. There was no recurrence of VOC, stroke, or ACS. Most patients from Africa were able to return home after one year. Most patients resumed normal school activity and improved their learning performances. Growth and development varied according to sex and age at transplantation and some patients needed hormone replacement.

Walters et al[68]reported late neurologic outcome in children with severe SCD who underwent transplantation between 1991 and 2000. After HSCT, patients with stroke who had stable engraftment of donor cells experienced no subsequent stroke events after BMT, and brain magnetic resonance imaging exams demonstrated stable or improved results. However, two patients with graft rejection had a second stroke after BMT. In a literature review Bodas et *al*.[69] reported the neurological long-term outcomes following myeloablative HSCT in 81 patients with history of cerebrovascular abnormalities on imaging prior transplant. Two of these patients experienced transient ischemic attacks during or post-transplant. From patients with follow-up cerebral imaging, 71% had stable imaging, 13% had improved imaging, and 16% showed progressive neurovascular abnormalities on imaging over the short term after HSCT.[69] Patients who underwent neurocognitive testing showed a non-statistically significant trend toward improvement in IQ. From the 22 patients who underwent matched sibling donor or haploidentical HSCT, reported by Dallas et al.[70] no patient with sustained engraftment exhibited any post-transplant clinical evidence of a cerebral vascular accident or progression on imaging studies. Magnetic resonance imaging showed improvement in white matter changes, and magnetic resonance angiogram revealed stable or even improved vessel abnormalities. Transcranial doppler showed a significant decrease in maximal velocity, in comparison with pre-transplant value and were normal at the last evaluation. Comprehensive neuropsychiatric evaluations show stable cognitive function after transplant. Since most patients had improvement or stabilization of their neurological disease transplant, long term comparison with no transplant patients are needed.

Two reports give data on long term pulmonary outcome in patients transplanted with previous pulmonary function abnormalities. They concern children with obstructive or restrictive pre-transplant syndromes, but there is no data evaluating the post-transplant outcome of patients transplanted with pulmonary hypertension. In a long-term follow-up of children transplanted after a myeloablative regimen, most patients with pre-transplant obstructive or restrictive syndrome displayed a stabilization (38%) or improvement (46%) of their pulmonary function.[68] In the experience reported by Dallas *et al* in children transplanted from matched or haploidentical related donor, 12 of the 16 patients had stable or improved pulmonary function tests. [70]

Therefore, HSCT seems to limit the progression of organ damage from the natural course of severe SCD; however, future studies are needed to evaluate post-transplant outcome in larger cohorts of patients including adults in a more systemized fashion.

Fertility has long remained an area of concern for both patients and their families and sometimes deters them from pursuing HSCT. The risk of infertility after HSCT depends on the conditioning regimen, gonadotoxic chemotherapeutic agents, and stage of pubertal development at the time of HSCT.[68,71] In the report of Walters, long-term follow-up evaluations of SCD patients who underwent HSCT with myeloablative conditioning found that, of the evaluable patients, 9/13 males had normal follicle-stimulating hormone and luteinizing hormone levels, but only 3/13 had normal testosterone levels. Among females, 8/14 had primary ovarian failure.[68]Dallas et *al*.[70] have monitored endocrine function after HSCT in patients of age ≥12 years. Five of the nine males exhibited normal endocrine gonadal function and 4 males had evidence of hypogonadism. There was no data concerning sperm examination. Two of the four females developed ovarian failure with elevated gonadotropin and low estradiol levels requiring replacement therapy. The other two females had normal laboratory results and menstrual cycles, and one of the women was 5 months pregnant at her last evaluation. Improvements in reproductive medicine techniques have offered more individuals the option of fertility preservation. Although there is limited data, fertility preservation has been successful

in both males (cryopreservation of sperm or testicular tissue) and females (preservation of embryos, mature oocytes, and ovarian tissue) with SCD prior to HSCT.[72–76] One hopes that with the use of non-myeloablative regimens and improvement of techniques to improve fertility preservation, the benefits of HSCT to those with SCD will outweigh the risks.

The table below summarizes data of literature concerning late effects after HSCT for SCD *(Talano , European Journal of Haematology 2014).*

Table 2 Late effects after AlloHSCT for SCD

Author	*n*	Neurological findings	Pulmonary function	Gondal function
Walters (11)	55	29 CVA prior to BMT, 27 patients had stable neurological findings post-BMT (2 patients who rejected had progressive disease)	FEV1 and FVC improved after BMT; 10 of 11 patients with restrictive disease were stable or improved	3 of 13 males had normal testosterone; 8 of 14 females had primary ovarian failure
Bodas (12)	81	79 of 81 had no TIA/CVA post-BMT 38 of 45 had stable to improved MRI post-BMT	NA	NA
Dallas (13)	22	No CVA/TIA post-BMT. Stable to improved MRI. TCD normalized in all patients	12 of 16 patients evaluated had stable to improved PFTs	5 of 9 males had normal gonadal function 2 of 4 female had ovarian failure

2.1.6 Age impact in HSCT for SCD

As reported by Gluckman et *al.*[2], in HLA-matched sibling HSCT from the European Blood and Marrow Transplant, Eurocord, and the CIBMTR, event free survival was lower with increasing age at transplantation. This finding is also usually reported in transplants for other non-malignancies or malignancies diseases. In this large series, 73% of adults received a myeloablative conditioning regimen. The 5-year OS was 95% (95% CI, 93%-97%) and 81% (95% CI, 74%-88%) for patients younger than 16 years and those aged 16 years or older, respectively (P<0.001); the corresponding EFS was 93% (95% CI, 92%-95%) and 81% (95% CI, 74%-87%; P<0.001). There is no impact of age on graft failure but increased GVHD incidence with age which could lead higher transplant-related mortality. For every 1-year increment in age at transplantation, there was a 4% increase in the HR for acute GVHD. In multivariate analysis, age over 16 years is associated with higher incidence of chronic GVHD. The increased post-transplant mortality observed in adults may also be explained by the more frequent pre-transplant organ damages[77][Capelli ASH 2017]. However, comparisons between pre-transplant comorbidities in the pediatric and adult population are lacking. In the series of HSCT in adults, reported by Hsieh *et al*, most patients had pre-transplant comorbidities (TRV>2.6 m/s in 43% of patients, sickle nephropathy with serum creatinine ≥1.3 mg/dL in 13%, serum ferritin >1000 ng/mL in 50%, hepatopathy in 20% and DLCO <50% in 10%).[4] However, despite high pre-transplant comorbidities reported in these patients, the use of non-myeloablative transplant allowed to limit transplant toxicity.[4]

2.2 Existing knowledge relating to the condition under investigation

The experimental arm of the study is the transplant arm. Transplantation will be a non-myeloablative transplant from related HLA matched donor as previously reported by the NIH group[3].

This approach of HSCT is based on myelosuppression with tolerance induction. The NIH group aimed to develop a regimen that would allow sufficient myelosuppression to achieve the modest levels of donor myeloid chimerism required for disease reversion while also achieving immunologic tolerance through pharmacologic manipulation. Several regimens tested in patients with SCD could fit this classification. Indeed, the work of Ianonne et *al.* [78] in which they used 200 cGy of TBI, fludarabine, and immunosuppression with cyclosporine, showed that patients had temporary donor engraftment. However, when cyclosporine was tapered as per

protocol, donor grafts went to undetectable levels, suggesting that immune tolerance had not been achieved. Realizing the important finding of this study, they chose a low-dose radiation approach, but used sirolimus (rapamycin) instead of cyclosporine, on the basis of a novel mechanism of tolerance induction. Unlike calcineurin inhibitors (eg, cyclosporine and tacrolimus), sirolimus does not block T-cell activation (signal 1) but binds to the mammalian target of rapamycin blocking proliferation (signal 2). Signal 1 in the absence of signal 2 renders T cells anergic, promoting T-cell tolerance.[79] In a murine peripheral blood stem cell low-dose TBI transplantation model comparing a 30-day course of CSA to sirolimus, long-term, high level chimerism was attained only in sirolimus-treated mice, and mixed lymphocyte reactions demonstrated tolerance to donor cells. Correction of disease was also demonstrated in sickle cell transgenic knockout mice by use of the sirolimus-based regimen.[80] Given the expected decrease risk of graft failure after G-CSF–mobilized peripheral blood compared to bone marrow as the source of HSCs, along with the 50% probability for heterozygosity for the sickle mutation among sibling donors, and the known adverse effects of G-CSF mobilization in SCD the NIH group initiated a prospective, controlled clinical trial of peripheral blood hematopoietic stem cell mobilization and processing in patients with sickle cell trait with age- and race-matched controls.[81,82] Symptoms were similar between the 2 arms, and there was no evidence for G-CSF–induced sickling in subjects with sickle cell trait. HSC mobilization and collection, also were similar. [83]

Then, they built their protocol on the previous nonmyeloablative experiences for adults using a conditioning regimen based on a 300 cGy of TBI.[78,84] As additional GVHD prophylaxis, they chose alemtuzumab (1mg/kg) over antithymocyte globulin for better toxicity profile in patients with SCD and superior prophylaxis against GVHD.[85,86] Within days of administration, alemtuzumab depletes majority of circulating host and infused donor lymphocytes. Alemtuzumab remains detectable for several weeks and further deletes alloreactive T cells during subsequent donor engraftment and initial immune. They hypothesized that long-term administration of sirolimus (for 6-12 months) could then further induce sufficient number of regulatory T cells to promote tolerance in a mixed chimeric setting during the remainder of donor immune reconstitution to reduce delayed GVHD. Thus low-dose TBI, alemtuzumab, and sirolimus theoretically provide the necessary environment for stable mixed chimerism and minimal GVHD.

Ten adults transplanted with this protocol were initially reported in the NEJM in an non controlled study.[3] All patients tolerated the conditioning regimen and were alive at the last follow-up. All but one had long-term donor engraftment. No patient experienced acute or chronic GVHD. The kinetics of donor myeloid chimerism were rapid and reached nearly 100% early in the majority of patients, whereas the kinetics of donor T-cell engraftment was less rapid and reached a plateau after 12 months. No patient reached 100% donor chimerism in both compartments, and immunosuppression was continued on the basis of the initial withdrawal plan requiring full donor lymphoid chimerism in the absence of GVHD, but a modification of this plan to allow tapering with lymphoid chimerism levels of 50% or greater has allowed the withdrawal of immunosuppression in 4 patients. These 4 patients continue to demonstrate stable mixed chimerism in the absence of immunosuppression. The mixed chimeric state allowed complete replacement by donor-type hemoglobin to levels that gradually improved to the normal range post-HSCT. Importantly, the replacement by donor type red cells allowed complete withdrawal of chronic narcotic therapy.

At time, the NIH group has reported 30 adult patients aged 16-65 years with severe disease enrolled in this nonmyeloablative transplant study. Twenty-six of them retained their graft resulting in normalization of their hemoglobin level. The mean donor T-cell level was 48% (95%CI, 34%-62%); the myeloid chimerism levels, 86% (95%CI, 70%-100%). Although no patient achieved 100% donor chimerism in both T- and myeloid cells, sirolimus was discontinued in 15 of 26 engrafted patients with continued stable donor chimerism and no graft-vs-host disease. Twenty-six patients (87%) had long-term stable donor engraftment without acute or chronic graft-vs-host disease. One patient died of intracranial hemorrhage after graft rejection. The normalized hemoglobin and resolution of hemolysis among engrafted patients

were accompanied by stabilization in brain imaging, a reduction of echocardiographic estimates of pulmonary pressure, and allowed for phlebotomy to reduce hepatic iron. The mean annual hospitalization rate was 3.23 (95%CI, 1.83-4.63) the year before, 0.63 (95%CI,0.26-1.01) the first year after and 0.19 (95% CI, 0-0.45) the second year after transplant.[4]
These results were confirmed by another group evaluating the same protocol in 13 adults with severe SCD, including 2 cases that were ABO incompatible.[5] All 13 patients initially engrafted. A stable mixed donor/ recipient chimerism was maintained in 12 patients (92%), whereas 1 patient not compliant with sirolimus experienced secondary graft failure. With a median follow-up of 22 months (range,12 to 44months) there was no mortality, no acute or chronic graft-versus-host disease (GVHD), and no grades 3 or 4 extramedullary toxicities. At one year after transplantation, patients with stable donor chimerism have normalized hemoglobin concentrations and improved cardiopulmonary and quality of life including bodily pain, general health, and vitality. In 4 patients, sirolimus was stopped without rejection or SCD-related complications.
More recently this approach was also evaluated by 2 other groups: Guilcher et *al.*,[6] in 14 children and Alzahrani [Alzahrani EBMT 2018] in 24 patients aged from 14 to 39 years.
In the experience reported by Guilcher et *al.* the event-free survival was of 100% and no patient presented GVHD. At the last follow-up, 8 patients were off sirolimus, 1 was weaning. Only 2 patients over 1-year post-HCT had not initiated sirolimus weaning. In the experience reported by Alzahrani, of 24 patients with a short follow-up (median 190 days (range 5-970), engraftment occurred in 23 patients, there was no GVHD and no transplant related mortality.
Finally, when we pool the experience of the 4 groups, a total of 81 patients were transplanted with the NIH approach. Ninety-two percent of patients were cured with normalized hemoglobin levels, resolution of hemolysis and stable hemoglobin. No death was related to transplant, 1 death was due to SCD and only 6 (7.4%) graft failures were reported. No patient presented GVHD. In our unit of hematology for adolescents and young adults of Saint Louis hospital, we transplanted 3 patients with this approach: all engrafted and presented a mixed chimerism in the whole blood cells population and in the T lymphocytes subset at last follow-up (6, 8 and 12 months) They all have the same level of HB S in comparison with their donor; none presented GVHD or severe post-transplant complications.
These results underscore the successful use of a chemotherapy-free regimen in matched related HSCT for high-risk SCD in children and adults, and demonstrates a high cure rate, absence of GVHD or mortality, and improvement in quality of life. However, the relatively small numbers and mixed chimeric state do warrant larger trials with extended follow-up. Longer follow-up would also allow exploration regarding whether reduced intensity conditioning regimens are associated with less infertility and organ toxicity, compared to myeloablative transplants.

2.3 Hypotheses for the research

Despite marked advances existing in the management of SCD, most adult patients develop a chronic debilitating condition with progressive organ damages and early deaths. HSCT can cure adults with SCD, but patients older than 16 years, mostly with significant sequela of SCD, including organ dysfunction, are often excluded in regard to transplant-related mortality expected after myeloablative conditioning regimen and to the risk of GVHD. Today less intense preparative regimens have made curative approaches available to adults, as reported by the NIH group and Saraf et *al.* with a non-myeloablative conditioning regimen, associating alemtuzumab and low dose TBI followed by post-transplant sirolimus. As detailed in the previous paragraph, these results are very encouraging, but there are no data comparing outcome of transplanted patients with patients not transplanted, allowing to assess the long term superiority of matched related HSCT over with standard care in adults with severe SCD. We design here a prospective multicenter trial targeting patients over 15 years with severe SCD, and compare non myeloablative transplant (when a MRD is identified) versus no HSCT (for

patients lacking MRD). We hypothesize that long-term survival without GVHD and without SCD complications will be superior in the transplant arm.

2.4 Originality and innovative aspects

Matched related HSC transplant is not a standard of care in adults with severe SCD because to the expected toxicity related to the procedure in patients with comorbidities. From the 1000 matched related transplants for SCD performed in the world and recently reported, only 154 patients were older than 15 years.[2] Recent reports on non-myeloablative (NMA) transplant from a MRD highlight the safety and efficacy of this approach in adults. However, the place of this procedure remains controversial in SCD adult patients.
As standard of care (ie, non-transplant therapies) has low toxicity, benefit of HSCT has to be evaluated in regard to no-transplant outcome. To date, few studies have prospectively compared HSCT versus other treatments, leaving physicians without adequate information upon which to base specific therapeutic decisions. The ideal comparison between these 2 very different treatments would be a randomized trial of the treatment options. However, such trials are difficult to conduct and are usually lengthy, as less than a third of potentially eligible patients will have a suitably HLA-matched donor. An alternative approach is the concept of donor versus no donor comparison, according to the availability of a suitably matched donor. One such French trial "drepagreffe" has compared, in children with accelerated velocity assessed by TCD, matched related myeloablative transplantation in patients with a donor with chronic transfusion in patients who did not [Bernaudin submitted to the JAMA]. Another donor (matched related and unrelated) versus no donor study was recently opened in the United States (NCT02766465), including patients from 15 to 40 years transplanted after a myeloablative conditioning regimen associating high dose busulfan, fludarabine and ATG. To date, there is no study which prospectively compares non myeloablative transplant with conventional approaches in severe SCD. Here, we propose to compare, in patients over 15 years with severe SCD and an available MRD, a HSCT using a NMA conditioning regimen versus standard of care in patients without a MRD. We believe such a trial would be pivotal to better define the optimal treatment options for SCD adultsand to evaluate a curative option. Our goal is to demonstrate the safety and the superiority of HSCT using NMA conditioning compared to standard of care in these patients.

2.5 Description of the population of research participants and justification for the choice of participants

The study plans to include adolescents and young adults (aged from 15 to 45 years) with severe SCD and at least one non-SCD sibling > 16 years from the same parental couple.

Justification of age of patients included: children are not included in the study, considering the excellent results of myeloablative transplant in this population. Today, myeloablative conditioning transplant remains the recommended modality of transplant in children. In the opposite, as reported by Gluckman et *al.*[2], event free survival was lower with increasing age and GVHD incidence was higher. The increased post-transplant mortality observed in adults may be explained by more pre-transplant organ damage. Most adults of this series were transplanted after a myeloablative conditioning regimen. As previously reported by others, we hypothesize a decrease transplant related mortality and GVHD, using in SCD adults, a reduced conditioning regimen and a post-transplant immunosuppression by sirolimus.[4,5,60]

Justification of the pre-transplant complications related to SCD: patients have to present at least one of the following criteria:

- history of 2 VOC requiring hospitalization over one year within the past 2 years

- at least 1 severe ACS within the past 2 years defined as followed: ACS requiring red cell transfusion, or hospitalization in intensive care unit, or ACS with PaO2 < 60 mmHg or arterial blood PH < 7.35 or PaCO2 > 50 mmHg or need more than 4 liters of 02/ mn for reaching Sat02 > 98%
- 1 VOC requiring hospitalization over the last 2 years and history of recurrent ACS (three or more)
- history of ischemic stroke or cerebral/cervical arterial stenosis ≥ 25% or apparition of silent infarct in the last 2 years
- pulmonary hypertension defined by mean pulmonary artery pressure ≥ 25 mmHg at rest, determined by right heart catherization
- osteonecrosis of at least 2 joints including one diagnosed in the past 2 years.
- sickle nephropathy (estimated glomerular filtration rate (by CKD EPI formula) <100 ml/min/1.73M2 and persistant microalbuminuria (microalbuminuria/creatininuria ratio >10 mg/mmol) without other cause of nephropathy)

Most of these complications are considered as transplant indication in most studies or recommendations (see paragraph 2.1.3.1 indications). They mostly lead to increase mortality and morbidity, even treated with best recommended therapy. Indications for matched related transplant in SCD adults have been discussed with French specialists of SCD.

In our inclusion criteria, pulmonary hypertension will be defined by mean pulmonary artery pressure ≥ 25mmHg determined by right heart catherization. Elevated TRV, >2.5, 2.7 or 2.8 m/sec, identifying SCD patients at risk for pulmonary hypertension, has been regularly recognized as an indication for HSCT, as it is associated with a marked increase in mortality rate. However, the elevated mortality with high TRV is largely driven by the subset of patients that do have pulmonary hypertension. Pulmonary hypertension concerns mostly adults with a minimal prevalence of 10%.

Justification of pre-inclusion treatment: At the inclusion, patients may be or not treated with hydroxyurea or chronic transfusion therapy. Currently, most patients transplanted for VOC or ACS, had previously been treated by hydroxyurea. In this comparative prospective "transplant versus no transplant" trial, we chose to also include patients who were never treated by hydroxyurea, in regard to the low toxicity expected after the reduced intensity conditioning transplant.

Patients already receiving chronic transfusions for VOC or ACS not responding to hydroxyurea, will be eligible, provided at least 3 VOC requiring hospitalization over one year within the past 2 years before initiation of chronic transfusions, and at least a history of an ACS: because chronic transfusion has been shown to significantly decrease VOC and ACS (2 randomized controlled studies), these patients might escape the inclusion criteria (i.e.at least 3 VOC requiring hospitalization over one year within the 2 past years before inclusion), although representing a group with severe disease. As far as they fulfilled the inclusion criteria, within the 2 years before initiation of chronic transfusions, we suggest they will be eligible.

Justification of need to have at least one non-SCD sibling > 16 years from the same parental couple:

It gives a possibility of an HLA matched sibling > 16 years

Interventions and products which will be performed or used as standard

Once the eligibility criteria and the informed consent have been obtained, HLA typing of the patients and their siblings (if not previously done) will be performed to identify potential HLA MRD. In patients with already HLA typing available, result of this typing can be used to determine the treatment arm (transplant or non-transplant). Patients with a HLA MRD will be transplanted and compared with other patients.

- Transplant group

a. Monthly red blood cell transfusions/exchanges will be performed during the three months before transplant. Hemoglobin S level target prior to the preparative regimen is < 30%
b. Stem cell source: Donors will receive 5 days of granulocyte colony-stimulating factor (filgrastim) mobilization (10 µg/kg/d from day-4 to day 0), followed by large-volume peripheral blood leukapheresis to collect a goal of 10×10^6 or more of CD34 cells per kilogram of the recipient's weight. If the number of CD34 cells is not obtained after one leukapheresis, a second will be planned, the next day to reach this goal.If the specifications of the final batch to be released were not met, in terms of cell number, the clinician may request a written exemption so that batches can be released. The batch can inclusion
c. not be released in case of technical problems or contamination.
d. Conditioning regimen: Alemtuzumab will be given as 0.03 mg/kg 7 days before, 0.1 mg/kg 6 days before, and 0.3 mg/kg 5, 4, and 3 days before transplant. A premedication by **methylprednisolone (1mg/kg) will be administrated before each alemetuzumab infusion.** Total-body irradiation of 300 rad will be given as a single dose 2 days before the procedure; radiation shielding will be applied to male gonads.
e. GVHD prophylaxis: Sirolimus will begin at D-1 at the initial dose of 5 mg every 4 hours for 3 doses, then 5 mg daily starting on day 0, modified to achieve target a trough level of 10 to 15 ng/mL for the first 3 to 4 months, near 10 ng/mL for the remainder of the first year. From 12 months post-transplant, sirolimus will be progressively tapered and stopped at 15 months post-transplant.
f. Peripheral blood stem cells will be infused on the day of the procedure.
g. When possible, platelet counts will be maintained at more than 50×10^9 /L and hemoglobin between 9 and 10 g/dL.
h. Supportive care will be the same usually performed after HSCT: antinfectious prophylaxis to prevent herpes virus reactivation (acyclovir), pneumocystis (sulfamethoxazole-trimethoprim in absence of G6PD deficient in donor), prompt evaluation and treatment for neutropenic fever, and frequent monitoring and preemptive treatment for cytomegalovirus DNA in the peripheral blood. Penicillin will given after cessation of systemic antibiotic associated with pneumococcal vaccination completion.

- No transplant group

  In the standard arm, patients who will not be transplanted, will receive the best standard care according to their situation and their previous treatment: initiation of hydroxyurea, continuation or optimization of the dose of hydroxyurea, initiation or continuation of transfusion program, initiation of a new drug proved to improve SCD and having authorization to use in France.

2.6 Interventions added for the research

HSCT

2.7 Name and description of the investigational product(s)

Peripheral blood stem cell from matched HLA related donor.

2.8 Description and justification of the dosage, route of administration, administration schedule and treatment duration

The transplant modalities will be the same as reported by the NIH group:

The conditioning regimen will consist on Alemtuzumab (1.03 mg/kg) associated with total-body irradiation of 300 rad with radiation shielding to male gonads.
The stem cell source will be PBSC from HLA-identical sibling donor with a goal of 10×10^6 or more of CD34 cells per kilogram of the recipient's weigh.
Sirolimus will be administered for GVHD prophylaxis during the first 12 months post-transplant. In the NIH protocol the sirolimus is continued until donor chimerism reaches 50% in Thymphocytes. However, there are no data showing the impact of T lymphocyte chimerism on myeloid chimerism and on stable engraftment in HSCT for non-malignancies. In the setting of HLA-identical sibling myeloablative transplant for SCD, it has been shown that myeloid chimerism (CD14 for monocytesand CD15 for neutrophils) could predict red cell chimerism and cure of the disease independently of the T cell chimerism (Confidential data, *A Magnani, M Cavazzana*, Necker, Paris France). Considering these important data, we chose to discontinue the sirolimus at 12 months of transplant whatever the level of T chimerism.

2.9 Summary of the known and foreseeable benefits and risks for the participants

In the transplant arm, the benefit expected is the cure of the disease, ie absence of post-transplant new complications related to SCD.

Some of the most common toxicities associated with the transplantation (including the reduced conditioning regimen and GVHD prophylaxis) are:

- Graft versus host disease according to the revised Magic consortium 2016 criteria
- Chronic GVHD according to the NIH classification (Appendix 20.4)
- Infection
- Fever, aplasia, pancytopenia, neutropenia, thrombopenia, anemia
- Gastrointestinal: nausea, vomiting
- Neurological disorders: visual disorders
- Cardiovascular: arterial hypertension
- Miscellaneous: serum sickness (skin rashes, pain and swelling of the joints) and anaphylaxis (hypotension, difficulty breathing and severe hives, mucositis)

The risks of transplant are severe GVHD, transplant related mortality or morbidity due to organ toxicity related to conditioning or immunosuppression therapy or infections. In the 81 patients currently reported in the literature, using the same modalities of transplant, no toxic death and no GVHD were reported. The impact on fertility of the conditioning regimen and of the post-transplant treatment by sirolimus has to be evaluated; in the NIH series, 4 women and 4 men among the 30 patients transplanted were able to have a total of 10 children naturally after transplant (Hsieh, personal data). Due to the absence of data about the effect of sirolimus on fetal development in human, an adequate contraception will be recommended during treatment by sirolimus to prevent pregnancy and continue its use for at least 12 weeks after the last sirolimus.

In the no-transplant arm, the risks are the complications of the disease despite the best supportive care including hydroxyurea and transfusions programs. Chronic transfusions can lead to iron overload and alloimmunization. Hydroxyurea can lead to fertility impairment.

3 OBJECTIVES OF THE RESEARCH

3.1 Main objective of the research

The main objective is to assess the benefit of HSCT on the 2-year event free survival calculated from inclusion, compared to standard care.

3.2 Secondary objectives

a) Compare in the both groups at 2 years:

- Overall survival,
- Total days requiring hospitalization after the first 5 months post-inclusion,
- Acute complications of SCD: VOC, ACS, priapism,
- Stroke, silent infarct, cerebral or cervical stenosis on MRA/MRI,
- Hemolytic index, hematologic and biochemical parameters,
- Organ function (kidney, eyes, heart, lung, liver, bone),
- Grade III-IV Infectious complications,
- Need for transfusion from 6 months post-inclusion,
- Alloimmunization rate,
- Iron overload,
- Chronic used of oral opioids,
- Nutritional involvement,
- Gonadic function and fertility,
- Quality of life,
- Anxiety and depression,
- Cost.
- Evaluate in the transplant group: chimerism, engraftment, GVHD.

4 DESCRIPTION OF THE RESEARCH

4.1 Primary endpoint

The 2-year event free survival.
An event is defined as:

a) death from any cause,
b) or an acute grade II-IV GVHD according to the Magic consortium 2016 (Appendix 20.3) classification or a moderate or severe chronic GVHD according to the NIH classification (Appendix 20.4),
c) or 3 hospitalizations for VOC defined according to usual criteria,
d) or one ACS defined by usual clinical criteria and a pulmonary infiltrate on chest film and/or thoracic computed-tomography (CT) scan,
e) or a stroke defined as a clinical event confirmed by an MRI, or a cerebral or cervical stenosis >25% in a new territory, or increase >25% of previous stenosis evaluated MRI and MRA or apparition of a silent infarct
f) or increased of at least +10% of tricuspid regurgitation velocity, (confirmed by 2 echocardiographies performed with a delay of at least 3 months) compared with pre-inclusion value for patients with TRV ≥2.7 at inclusion,

4.2 Secondary endpoints

- Death from any cause,
- Number of days requiring hospitalization at 1 and 2 years post-inclusion with exclusion of the 5 first months post-inclusion. (We plan to not count the days of hospitalization during the first 5 months post-inclusion considering that HSCT will be performed with a median delay of 3 months after inclusion and considering the time of hospitalization need for transplant),
- Clinical adverse events: number of VOC and ACS requiring hospitalization, number of hospitalization in intensive care unit,
- Number of priapism at 1 and 2 years post-inclusion,
- Number of stroke episodes at 1 and 2 years post-inclusion,
- Changes in biological parameters: LDH, aminotransferase, gamma-GT, alkaline phosphatase, bilirubin, TP, TCK, hemoglobin level, hematocrit, mean corpuscular volume, percentage of hemoglobin variants, reticulocyte, white blood cells and platelets counts, estimated glomerular function rate:

  →every 3 months from inclusion to 24 months in the standard arm.

  →in the transplant arm, these tests will also be made at M1, M2 and M3.

- Microalbuminuria/creatininuria ratio at M3, M6, M12, M24,
- Ferritin and transferrin saturation level at M3, M6, M12, M24,
- Gonadic function at 24 months: LH, FSH in men and women, testosterone and spermogram in men, oestrogen and AMH in women, Incidence of amenorrhea in women. Number of parity. In women, the evaluation of the ovarian function will be performed after 3 months of hormonal treatment cessation,
- Eye function: change in retinopathy status (appearance, disappearance, improvement, aggravation) at M12 and M24. Other eyes involvement (keratitis, uveitis),
- Heart (pulmonary hypertension, auricular or ventricular dilatation, left ventricular mass and function) by a transthoracic echocardiography. Explored data will be tricuspid regurgitant jet velocity, left atrial and ventricular dimension indexed to body surface, ventricular mass index and left ventricular ejection fraction. At M12 and M24,
- Lung function (pulmonary function tests, 6 min walk test). At M12 and M24,
- Bone function: new episode of avascular osteonecrosis and location, episode(s) of fracture,
- Central nervous system function: (magnetic resonance imaging with MRA/MRI) at M24,
- Liver and heart magnetic resonance imaging for iron overload evaluation in patients with ferritin > 1000 microg/L at the inclusion, M12 and M24,
- Number of red blood cell packed transfused from 6 months post-inclusion; (Pre and early post-transplant transfusion are a standard of care and may not be counted),
- Number of delayed hemolytic transfusion reaction (DHTR) (defined associated with hemoglobinuria/dark urine in the month following transfusion +/- bone pain with increased hemolytic markers and drop in HbA or new RBC allo-Ab) and new RBC alloantibodies assessed at M3, M6, 12 and M24,
- Oral opioid consumption by a diary recall questionnaire during the 24th and last month of follow up assessed at M3, M6, 12 and M24 at each medical visit, (Addenda 20-3),
- Quality of life questionnaire (MOS SF 36) assessed at M3, M6, 12 and M24, (Addenda 20-3),
- Hospital Anxiety and Depression Scale (HADS) questionnaire assessed at M3, M6, 12 at each medical visit, (Addenda 20-3),
- Change in weight at M3, M6, 12 and M24, at each medical visit and height at and M24,
- Severe infections (CTAE score: grade 3-4),
- GvHD incidence and grading (Magic consortium 2016 (Appendix 20.3) and NIH classification) in HSCT patients,

- Chimerism in HSCT assessed on total blood population and T subset at M1, M2, M3, M6, M9, M12, M18 and M24 and then every 6 months to M48.
- Cost: evaluated by the days of hospitalization from the inclusion,

5 DESCRIPTION OF RESEARCH METHODOLOGY

5.1 Design of the study

This is a phase 3 study. The design is a comparative controlled quasi-experimental (genetic randomization) cohort study with 2 groups of patients:

- "Exposed" patients are patients with an HLA identical sibling identified who will receive HSCT.
- "Unexposed" are patients lacking an HLA identical sibling who will receive standard of care.

We anticipate 30% of matched-related donors among siblings, so a 1:2 ratio between exposed and unexposed group.

5.2 Number of participating sites

Thirty seven valued centers in France will participate to the study and will recruit patients.
Out-patients will be recruited on the site taking them in charge for their SCD and addressed to a center transplant if HSCT will be planned.

5.3 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

6 IMPLEMENTATION OF THE STUDY

The start of the clinical trial is the inclusion date of the first patient.

6.1 Schedule for the study

- Enrolment period: **4 years**
- Duration of participation by each patient: **2 years**

Total study duration: **6 years**

6.1.1 Screening visit

Methods for informing and obtaining consent from the research participants

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
The participant; *an appointed representative*	*Principal Investigator or a declared collaborating doctor who has been trained in the research (state the specialist area)*	*Screening visit*	*Before baseline study*

The screening includes the assessment of the eligibility criteria and absence of exclusion criteria. Screening can be accessed by exams performed in the last 12 months. After screening, it recommended that the patient will be addressed to an investigator in charge of transplant to receive informations about HSCT. Then, study will be proposed to the patient.

- The absence of exclusion criteria has to be assessed as followed: Performance status
- Pulmonary function: FEV1 et FVC< 50% of the theorical value
  Post capillary and severe pre-capillary pulmonary hypertension with measured mean pulmonary artery pressure at rest >35 mmHg; Right heart catherization will be recommended in patients with TRV $\geq$ 2.7
- Left ventricular ejection fraction $\leq$ 45%
- Estimated glomerular fraction rate (GFR) < 50ml/mn /1.73m^2
- Conjugate bilirubin > 50 µmole/L, cirrhosis, ALAT>4N
- Uncontrolled infection
- Known hypersensitivity of alemtuzumab
- Known hypersensitivity to murin proteins and to the following excipients: disodium edetate, polysorbate 80, potassium chloride, potassium phosphate monobasic, sodium chloride, dibasic sodium phosphate, water for injections
- Positivity for HIV
- Pregnancy or breast-feeding women
- Alloimmunization or Delayed Hemolytic Transfusion Reaction precluding red cell transfusions whatever the time of occurrence
- Pregnancy at time of inclusion
- Alloimmunization or Delayed Hemolytic Transfusion Reaction precluding red cell transfusions

6.1.2 Baseline visit

After inclusion in the study, HLA typing will be performed to identify potential HLA MRD, and the following data have to be collected. Morphological explorations performed in the last 6 months can be considered for baseline visit. Other explorations should be performed in the 2 months after inclusion

- Past medical history of SCD complications (VOC, ACS, stroke, silent infarct, pulmonary hypertension, retinopathy, nephropathy, osteonecrosis, hepatopathy related to SCD, priapism, oral opioid consumption.
- Number of hospitalizations during the last 2 years, hospitalization in ICU,

- Quality of life questionnaire (MOS SF36), Hospital Anxiety and Depression Scale (HADS) (addenda 20-3)
- Indication for trial participation
- Treatment on going
- Medical clinical examination (ECOG, blood pressure, weight, height, general examination)
- Biological parameters: LDH, aminotransferase, gamma-GT, alkaline phosphatase, bilirubin, PR, APTT, hemoglobin level, hematocrit, mean corpuscular volume, reticulocyte count, percentage of hemoglobin variants, white blood cells and platelets counts, estimated glomerular function rate, microalbuminuria/creatininuria ratio. Erythrocyte group. RBC alloantibodies. Ferritin and transferrin saturation level
- Spermogram at time of sperm storage in men if patients not already treated by hydroxyurea. For other patients treated by hydroxyurea, we will collect results of spermogram performed before onset of hydroxyurea at time of the sperm storage. Dosage of LH and FSH, in both men and women, testosterone in men, oestrogen AMH and inhibin in women. Amenorrhea in women. Number of parity.
- Examination of the retina
- Heart (pulmonary hypertension, auricular or ventricular dilatation, left ventricular mass and function) by a transthoracic echocardiography. Explored data will be tricuspid regurgitant jet velocity, left atrial and ventricular dimension indexed to body surface, ventricular mass index and left ventricular ejection fraction.
- Lung function (pulmonary function tests, 6 min walk test)
- Pelvis radiography
- Central nervous system function: magnetic resonance imaging of the vessel and the parenchym at the inclusion and M24
- Liver and heart magnetic resonance imaging for iron overload evaluation in patients with ferritin > 1000 microg/L
- In the transplant arm: Blood sample for chimerism analysis, serology (B et C hepatitis, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV, HTLV-1 et 2, Toxoplasmosis (IgG et M), TPHA et VDRL, PCR for B, C hepatitis, HIV, and G6-PD dosage
- Oral consumption of opioids questionnaire

Patients with a HLA MRD will be transplanted and compared with other patients.

Fertility preservation and contraception in transplanted patients:

In men: considering the potential impact on fertility of the conditioning regimen including 3 Gy TBI [87] and of treatment by sirolimus, a sperm storage will be performed before transplant. In most patients receiving hydroxyurea, sperm storage has been performed before hydroxyurea initiation. It's important to stress the point that radiation shielding will be applied to male gonads to decrease the risk of post-transplant hypofertility. In pre-clinic models, no teratogenicity was reported with sirolimus (data from the CRAT: Centre de Référence sur les Agents Tératogènes).

In women: In theory, 3 GY ovarian radiation doesn't induce immediate post-treatment ovarian failure 90, but, there are few data concerning pregnancy after this conditioning 3-4. Considering that egg or ovarian pre-transplant conservation can be associated in

SCD patients with complications such as thrombosis, VOC and ACS, we don't propose systematically pre-transplant technic of fertility preservation. Decision for performing or not fertility preservation before transplant will take into account the results of pre-transplant ovarian function evaluation, age of patient, pregnancy wish and risk of the procedure. If necessary investigators can contact Pr C. Poirot (fertility preservation specialist: catherine.poirot@aphp.fr) for discussing indication of pre-transplant fertility preservation. For the patients who will not have fertility preservation before transplant, ovarian function will be monitor after transplant and post-transplant fertility preservation by egg storage could be proposed after sirolimus cessation. Contraception will be performed from the onset of conditioning regimen, continued during all the duration of treatment by sirolimus and could be stopped 12 weeks after the cessation of sirolimus.

6.1.3 Follow-up visits

In the non-transplant arm (standard care arm), visits of follow-up are planned every 3 months, until M24 (cf.6.2 Table or diagram summarizing the chronology of the research). Methods and measuring, collecting and analyzing the parameters for assessing safety described in the table are also performed every year post-transplant after M24 as part of the patient's care.

In the experimental arm, i.e., the transplant arm, the protocolary visits are planned every month during the first 3 months post-transplant and then every 3 months until M24, but patients may have more visits according to the usual management of transplant patients: generally every week during the first 3 months post-transplant, then monthly from 3 to 6 months post-transplant.

The tables below summarize the follow-up of the patients in both arms. Additional methods and measuring, collecting and analyzing the parameters for assessing safety described in the table for patients in the transplant arm are also performed every 6 months from M24 to M48 as part of the patient's standard of care.
Supplementary investigations, could be indicated during the follow-up, according to the medical situation of each patient, and will be left to the discretion of the physician.

6.1.4 Last study visit

The end of research visit is performed at M24 after infusion. This visit is not different from the other follow-up visits previously described.

At the end of the study, the patient is treated according to the usual care.

There is not expected exclusion period at the end of the study for the patient to participate on another research.

6.1.5 Early termination visit

This visit is not different from the other previously described visits (follow-up visit or last study visit).

In case of relapse, the patient is treated according to the usual care.

6.2 Table or diagram summarizing the chronology of the Study

To be noted the in the non-transplant arm (standard care arm), visits of follow-up are planned every 3 months, until M24.

	Inclusion (D-60*): D0	M1	M2	M3	M6	M9	M12	M15	M18	M21	M24	Every year post-transplant
Consent	X											
HIV serology	X											
Blood Pregnancy test in women	X											
Antecedent[1]	X											
Inclusion criteria	X											
Treatment on going	X			X	X	X	X	X	X	X	X	X
Clinical examination (ECOG, blood pressure, weight, height, general examination) (*after transplant only in transplant arm)	X	X*	X*	X	X	X	X	X	X	X	X	X
Quality of life questionnaire (MOS SF36), Hospital Anxiety and Depression Scale (HADS)	X			X	X		X				X	X
Questionnaire of oral consumption of opioids	X			X	X		X				X	
Urine test (microalbuminuria/creatininuria ratio)	X			X	X		X				X	X
SCD evaluation [2]	X						X				X	X
Central nervous system function MRI[3]	X										X	
Liver and heart magnetic resonance imaging for iron overload evaluation in patients with > 1000 microg/L	X						X				X	X
Gonadic function[4]	X						X				X	
Adverse events/serious adverse event (see Section 12)		X	X	X	X	X	X	X	X	X	X	

***** Morphological explorations performed in the last 6 months can be considered for baseline visit.
In absence of news symptoms, examination of the retina, transthoracic echocardiography, pulmonary function tests and 6 min walk test, pelvis radiography, performed in the last 6 months can be considered for baseline visit. In absence of neurological symptoms and in patients without previous cerebral vasculopathy, magnetic resonance imaging of the vessel and the parenchym performed in the last 12 months can be considered for baseline visit. Other explorations should be performed in the 2 months after inclusion.
1 ATCD of SCD complications (VOC, ACS, stroke, silent infarct, pulmonary hypertension, retinopathy, nephropathy, osteonecrosis, hepatopathy related to SCD, priapism, Oral opioid consumption. Number of hospitalizations during the last 2 years, hospitalization in ICU unit.
2 Retina examination, Heart (pulmonary hypertension, auricular or ventricular dilatation, left ventricular mass and function) by a transthoracic echocardiography. Explored data will be tricuspid regurgitant jet velocity, left atrial and ventricular dimension indexed to body surface, ventricular mass index and left ventricular ejection fraction, Lung function (pulmonary function tests, 6 min walk test), Pelvis radiography
3 Central nervous system function: magnetic resonance imaging of the vessel and the parenchym at the inclusion and M24
4 Spermogram (at inclusion, only in men not already treated by hydroxyurea), LH, FSH, testosterone in men, oetrogen in women; amenorrhea in women. Number of parity.

Patients included in the transplant arm will be monitored as usually performed after HSCT: classically, medical clinical examination every day, blood tests as followed: a) blood cell count every day; b) LDH, ferritin, aminotransferase, gamma-GT, alkaline phosphatase, bilirubin, TR, APTT, estimated glomerular function rate twice weekly, c) sirolimus level twice weekly d) viral replication of CMV, EBV, adenovirus weekly.

Investigators should pay special attention to the occurrence to adverse events potentially related to alemtuzumab: autoimmune hepatitis or severe impairment of hepatic function and haemophagocytic lymphohistiocytosis; alveolar hemorrhage, heart attack, ischemic or hemorrhagic stroke, dissection in cervical or vertebral arteries. When one of this complication will be suspected, exploration will be promptly performed for confirmation of diagnosis and for treatment initiation.
A supplementary follow-up is planned in the transplant arm as depicted in the table below.

Specific monitoring in the transplant arm

	M0 = HSCT	M1	M2	M3	M6	M9	M12	M15	M18	M21	M24	Every 6 M from M24 to M48 *
Pre-transplant biological analysis [1]	X											
Chimerism in total blood and CD3+ population		X	X	X	X	X	X	X	X	X	X	X
In the transplant arm: GVHD evaluation and infection evaluation		X	X	X	X	X	X	X	X	X	X	X
Blood test [2]	X	X	X	X	X	X	X	X	X	X	X	X
In the transplant arm: Analysis of immune reconstitution [3]				X	X		X				X	

1 Serology:s B et C hepatitis, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV, HTLV1-2

Toxoplasmosis (IgG et M), TPHA et VDRL, PCR for B, C hepatitis, HIV, HTLV-1 et 2, HIV, and G6-PD dosage.
2 LDH, aminotransferase, gamma-GT, alkaline phosphatase, bilirubin, TP, TCK, hemoglobin level, hematocrit, mean corpuscular volume, reticulocyte count, percentage of hemoglobin variants, white blood cells and platelets counts, estimated glomerular function rate. Erythrocyte group. Irregular agglutinin. Ferritin and transferrin saturation level
3 Gammablobulin level, CD4, CD8, CD19, NK cells and when possible memory, naïve subsets and T reg CD4+

Analysis by NGS (Next Generation Sequencing) of clonal myeloid hematopoiesis is recommended in peripheral blood before and two years after transplant in cases of mixed chimerism or rejection
* Standard of care

6.3 Distinction between standard care and study

Procedures and treatments to be provided during the study	**Procedures and treatments associated with <u>standard care</u>**	**Procedures and treatments added for the <u>study</u>**
Treatments	Supportive care including hydroxyurea and chronic transfusions	Conditioning regimen (TBI, alemtuzumab) HSCT GVHD prophylaxis (sirolimus) Hospitalization for 4 to 6 weeks

Consultations	3-month consultation until 24 months	Follow-up performed in the usual follow-up after HSCT: After discharge of hospital, every month during the first 3 months post-transplant and then every 3 months until M24 post-HSCT. (Patients may have more visits according to the usual management of transplant patients: generally every week during the first 3 months post-transplant, then monthly from 3 to 6 months post-transplant.)
Blood tests	Blood tests performed in the usual follow-up of patients with SCD according to the severity of disease and treatment	Blood tests performed in the usual follow-up after HSCT

6.4 Biological samples collection

Not applicable.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria of recipient

- SCD patients (SS/Sβ0)
- Aged :15 to 45 years
- With at least one non-SCD sibling > 16 years from the same parental couple
- Who presented at least one of the following criteria:

  - History of 2 VOC requiring hospitalization over one year within the past 2 years and at least a past history of an ACS

  - At least 1 severe ACS within the past 2 years defined as followed: ACS requiring red cell transfusion, or hospitalization in intensive care unit, or ACS with PaO2 < 60mmHg or arterial blood PH < 7.35 or PaC02 > 50mmHg or need more than 4 liters of 02/ mn for reaching Sat02 > 98%

  - 1 VOC requiring hospitalization over the last 2 years and history of recurrent ACS (three or more)

  - History of ischemic stroke or cerebral/cervical arterial stenosis ≥ 25% or apparition of silent infarct in the last 2 years

- Pulmonary hypertension defined by mean pulmonary artery pressure ≥ 25 mmHg at rest, determined by right heart catherization
- Osteonecrosis of at least 2 joints including one diagnosed in the past 2 years.
- Sickle nephropathy (estimated glomerular filtration rate (by CKD EPI formula) < 100 ml/min/1.73M^2 and persistant microalbuminuria (microalbuminuria/creatininuria ratio >10 mg/mmol) without other cause of nephropathy).

- Requiring treatment with Hydroxyurea or chronic transfusion, or already treated by Hydroxyurea or transfusion program (TP) at inclusion.
- For : Patients already receiving chronic transfusions for VOC or ACS not responding to hydroxyurea : they will be eligible, if they provided before the beginning of chronic transfusions at least :
  - 2 VOC requiring hospitalization over the last 2 years
  - At least 1 severe ACS within the past 2 years defined as followed: ACS requiring red cell transfusion, or hospitalization in intensive care unit, or ACS with PaC02 < 60mmHg or arterial blood pH < 7.35 or PaC02 > 50mmHg or need more than 4 liters of O2/mn for reaching Sat02 > 98%
  - 1 VOC requiring hospitalization over the last 2 years and history of recurrent ACS (three or more)
- Contraception during all the study period by sirolimus for women of child bearing potential
- Signed informed consent
- Amenable to HLA typing, HSCT if an HLA-identical sibling is available.
- Patients affiliated to the French health care insurance.

7.2 Exclusion criteria of recipient

- Performance status: ECOG scale>1
- Pulmonary function: FEV1 et FVC< 50% of the theorical value
- Pulmonary hypertension with measured mean pulmonary artery pressure at rest ≥ 35 mmHg. All patients with a TRV≥ 2.7m/s on cardiac Doppler (confirmed by 2 repeated measures with a 3 to 6 months period) will have to perform right heart catheterization, as recommended by the French guideline for management of adult SCD patients Pulmonary hypertension is confirmed if mean pulmonary pressure ≥25 mmHg at rest. Mean pulmonary

artery pressure at rest ≥ 35 mmHg appear as a marker of severity that could increase significantly the risk of HST.

- Cardiac ejection fraction ≤ 45%
- Creatinine clearance <50ml/mn /1.73m^2
- Conjugate bilirubin >50 µmole/L, active hepatitis, cirrhosis, ALAT>4N
- Severe uncontrolled infection
- Known hypersensitivity of alemtuzumab
- Known hypersensitivity to murin proteins and to the following excipients: disodium edetate, polysorbate 80, potassium chloride, potassium phosphate monobasic, sodium chloride, dibasic sodium phosphate, water for injections
- Positivity for HIV
- Pregnancy or breast-feeding women
- Alloimmunization or Delayed Hemolytic Transfusion Reaction precluding red cell transfusions. These specific cases will be discussed with SCD, transplant and transfusion specialists
- Previous solid organ transplant or hematopoietic stem cell transplant.
- uncontrolled hypertension
- history of arterial dissection of the cervicocephalic arteries
- history of angina pectoris or myocardial infarction

7.3 Inclusion criteria of donors

- Age: 16 to 60 years
- with Hb electrophoresis: AA, AS or AC, beta thalassemia trait
- Donor with usual clinical and biological eligibility criteria for G-CSF mobilization and peripheral blood stem cell collection including legal viral serologies assessment authorizing the transplant. A dosage of G6PD (+/- genotyping) will be performed.
- Being HLA identical with the patient
- Negative Covid-19 Test

In patient with several potential donors (several matched sibling donor), ABO matched donor will be chosen in priority.

7.4 Recruitment procedure

Out-patients will be screening by the physicians in charge of them for the treatment of SCD.

After screening, the patient will be addressed to an investigator in charge of transplant to receive informations about HSCT. Then, patients agreeing with the design of the study will be included by investigators in charge of them or physicians in charge of transplant.

The sites of recruitment are pediatric and adult units.

Patients will HLA matched sibling donor will be referred to transplant unit for HSCT.

Justification of sufficient recruitment capacity for the number of participants that need to be included:

	Number of subjects
Total number of subjects to be included	78
Number of valued recruiting sites	37
Enrolment period (months)	48
Number of subjects/site	2-7
Number of subjects/site/month	0,04

8 TERMINATION RULES

There are a number of possible situations

- Temporary suspension: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form CRF).
- Premature termination, but the participant remains enrolled in the study until the end of his/her participation: the investigator must document the reason.

8.1 Criteria and procedure for premature withdrawals of participants from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- If a participant exits the study prematurely, all data about that participant may be used until consent is withdrawn.

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- The case report form must list the various reasons why the participant exited or was withdrawn from the study:
  - Adverse reaction
  - Another medical issue
  - Personal reasons of the participant

- Explicit withdrawal of consent

- If a participant exits the study prematurely due to a serious adverse event, a serious adverse event notification form will be sent by mail to the sponsor. The serious adverse event will be monitored until it is resolved. The data and safety monitoring board (DSMB) can specify and/or validate the monitoring methods.

- After the start of the alemtuzumab treatment, if the patient:
  - suffers an adverse event of particular interest (see section 12.1.2.2.1),
  - has or develops a contraindication to alemtuzumab after first administration
  - experienced a treatment related disease considered as severe or evolving, the patient will be withdrawn from the treatment.

  Ending a subject's participation does not affect the normal management of the subject's illness in any way.

  Patient who withdraws from the alemtuzumab treatment will follow the entire trial as planned according to the protocol agenda.

8.1.1 Procedure for replacing participants

If a subject discontinues the study before the availability of the HLA tests, i.e. before the choice of treatment group, he will be replaced. Otherwise, all subjects will be included in the analysis.

8.1.2 Full or partial cancellation of the study

AH-HP as sponsor or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Safety Monitoring Board in the following situations:
- if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial.

Similarly, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.
AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

9 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

It is necessary for the investigators to refer at the mentions of the updated SmPCs (Summaries of Product Characteristics/RCP) of the Marketing authorization (AMM) or the protocol of the therapeutic use of the products (Alemtuzumab, Sirolimus, etc.). In this protocol for the management of patients, particularly with regard to contraindications, duration of contraception, dosage adjustments in case of toxicity monitoring of patients and drugs

prohibited or to be used with caution (refer to the website: **http://base-donnees-publique.medicaments.gouv.fr**, which presents the updated version of the SPCs for medicines).

Once the eligibility criteria and the informed consent have been obtained, HLA typing will be performed to identify potential HLA MRD. Patients with a HLA MRD will be transplanted and compared with other patients.

9.1 Standard arm

In the standard arm, patients who will not be transplanted will receive the best standard care according to their situation and their previous treatment: initiation of hydroxyurea, continuation or optimization of the dose of hydroxyurea, initiation or continuation of transfusion program, initiation of a new drug proved to improve SCD and having authorization to use in France.

9.2 Transplant arm

Patients should be transplanted within 1 to 6 months of inclusion.

a) Pre-conditioning therapy will be performed during the three months before transplant, in order to inhibit erythropoiesis . It will consist of Hydroxyurea administration (30mg/kg/j in absence of contraindication) associated with red blood cell exchanges targeting hemoglobin S levels under 30% during this period. In patients receiving déférasirox, this treatment will be withdrawn 2 weeks before the onset of conditioning regimen.
b) Stem cell source: Donors underwent 5 days of granulocyte colony-stimulating factor (filgrastim) mobilization (10µg/kg/d), followed by large-volume peripheral blood leukapheresis to collect a goal of 10×10^6 or more of CD34 cells per kilogram of the recipient's weight.
c) Conditioning regimen:
   - Alemtuzumab was given as 0.03 mg/kg at day -7, 0.1 mg/kg at day -6 days and 0.3 mg/kg at days -5, -4, and -3 days before transplant. A premedication by methylprednisolone (1mg/kg) will be administered before each perfusion of alemtuzumab. The infusion of alemtuzumab at the dose of 0.1 mg/kg or more (day -6 to day -3), will be performed in 2 to 6 hours according to the clinical tolerance. Blood pressure cardiac rhythm and oxygen saturation will be monitored every 30 minutes during alemtuzumab infusion. In case of significative changes in these parameters, the treatment by alemtuzumab will be interrupted, anelectrocardiogram will be performed and the patient will be strictly monitored until improvement of vital signs. Liver blood tests will be performed daily from day -7 to day -3 and after transplant 3 times per week, as usually in transplant recipient. In case of early side effects potentially related to alemtuzumab, pursuit of treatment will be discussed considering risk and benefit.
   - If possible, lymphocyte subsets monitoring before and after alemtuzumab administration, associated with alemntuzumab pharmakocinetic is recommended.
d) Total-body irradiation of 3 Gy was given as a single dose 2 days before the procedure; radiation shielding was applied to male gonads. GVHD prophylaxis: Sirolimus loading began the day before transplant, targeting a trough level of 10 to 15 ng/mL for the first 3 to 4 months, near 10 ng/mL for the remainder of the first year, Sirolimus will be progressively tapered from 12 months post-transplant and stopped at 15 months post-transplant.
e) Peripheral blood stem cells were infused on the day of the procedure
f) When possible, platelet counts were maintained at more than 50×10^9 /L and hemoglobin-between 9 and 10 g/dL.

Supportive care will be the same usually performed after HSCT: antimicrobial prophylaxis to prevent herpes virus reactivation (acyclovir), pneumocystis (sulfamethoxazole-trimethoprim), prompt evaluation and treatment for neutropenic fever. Prevymis will be administred as cytomegalovirus prevention in patient with CMV+ status associated with frequent monitoring for DNA in the peripheral blood, and eventually preemptive treatment.
Penicillin was given from day 0, until, at least, pneumococcal vaccination completion.

In case of GVHD, the treatment will be chosen by the investigator. Classically, the first-line treatment for an acute grade II-IV GVHD will be steroid (2mg/kg/day) and the first-line treatment for moderate or severe chronic GVHD will consisted on steroids (1mg/kg) Ciclosporin or tacrolimus should be avoided, especially in association with steroid due to the risk of PRES syndrome. In occurrence of graft rejection; patients will receive treatment for SCD according to the potential complications related to the disease. G-CSF may be used in case of prolonged neutropenia if necessary

9.3 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

Treatments that are not discouraged will be considered authorized. Some treatments will be used with caution due to drug interactions.

- **Concomitant treatments to Alemtuzumab:**

For the **ALEMTUZUMAB** (see RCP AMM Multiple Sclerosis), no formal drug interaction studies were conducted with **ALEMTUZUMAB** administered at the recommended dose for the treatment of multiple sclerosis (MS). In a clinical study in MS, patients who had recently been treated with interferon beta and / or glatiramer acetate had to discontinue treatment 28 days prior to initiation of **ALEMTUZUMAB**. There are no data specific to the use of **ALEMTUZUMAB** in allogeneic hematopoietic stem cell transplantation used with caution in view of drug interactions.

- **Concomitant treatment with Sirolimus (see cf RCP):**

Since Sirolimus is metabolised by CYP3A4, its absorption and elimination may be influenced by the substances that act on these proteins: ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin, rifampicin, rifabutin, verapamil, erythromycin, ciclosporin. In case of need to use those molecules, the Sirolimus dosages should be carried out at the initiation of these treatments.

- **Contraindicated or inadvisable treatment for patients with G6PD deficiency** and for patients whose donors have G6PD deficiency (see ANSM document 2013). Document attached in Addenda 20-4of the protocol.

10 EFFICACY ASSESSMENT

10.1 Description of Efficacy endpoints assesment parameters

An event is defined as:

a) Death from any cause,
b) Or an acute grade II-IV GVHD according to the Magic consortium 2016 (Appendix 20.3) classification or a moderate or severe chronic GVHD according to the NIH classification (Appendix 20.4),
c) Or 3 hospitalizations for VOC defined according to usual criteria
d) Or one acute chest syndrome (ACS) defined by usual clinical criteria and a pulmonary infiltrate on chest film and/or thoracic computed-tomography (CT) scan
e) Or a stroke defined as a clinical event confirmed by an MRI
f) Or a cerebral or cervical stenosis >25% in a new territory or increase >25% of previous stenosis evaluated MRI and MRA.
g) Or increased of at least +10% of tricuspid regurgitation velocity, (confirmed by 2 echocardiography performed with a delay of at least 3 months) compared with pre-inclusion value for patients with TRV≥2.7 at inclusion.

10.2 Anticipated methods and timetable for measuring, collecting and analyzing the efficacy data

In the non-transplant arm (standard care arm), visits of follow-up are planned every 3 months, until M24. In the transplant arm the visits are planned every month during the first 3 months post-transplant and then every 3 months until M24, but patients may have more visits according to the usual management of transplant patients.

11 SPECIFIC COMMITTEES FOR THE STUDY

11.1 Scientific committee

It includes: N Dhedin, JB Arlet, C Pondarre, A ZarourS. Chevret
Role: determine the objective, write the protocol, recommend changes to the protocol during the trial.

11.2 Steering Committee

A steering committee will be established, including the coordinating investigator (Dr N Dhedin), the scientific directors (Dr C Pondarre, Dr JB Arlet), the fertility preservation specialist (Pr C Poirot) and the biostatistician (Pr S. Chevret).
Role:

Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

Propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

11.3 Endpoint Adjudication Committee

An endpoint adjudication committee will be established.
Members: experts in charge of providing their uniform approval, blinded from the research interventions, of any clinical, biological, imaging endpoints, etc. needed to assess the primary and potential secondary endpoints. The members of this committee are not necessarily independent from the study (they may be investigators).

Roles: His mission is to review the clinical data in order to have a centralized review of the primary endpoint.

Operating procedures: Every 6 months

12 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

12.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational product.

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction**

Any adverse reaction for which the nature, severity or outcome is not consistent with the information related to the products, interventions and procedures used in the context of the clinical trial.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational product, modifications in the investigational product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.
For the clinical trials involving the first administration or use of an investigational product in healthy volunteers, any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational product, that may impact the safety of the trial subjects.
Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects

e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

12.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form eCRF.
The investigator must **document** serious adverse events **as thorough as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:

- *Common Terminology Criteria for Adverse Events [National Cancer Institute]*
- *For acute GVH: grading should be performed by the Magicconsortium* (Appendix 20.3) *criteria (Harris et al., 2016).*
- *For chronic GVHD: the NIH Consensus Criteria (Filipovichand al.BBMT, 2005).* (Appendix 20.4)
- *For infection: the GREFIG score.*

The investigator must assess the **causal relationship** between the serious adverse events and the study procedures [HSCT including reduced conditioning regimen (TBI, alemtuzumab) and GVHD prophylaxis] based on 2 causality terms choice (EVCTM method):
- related or,
- not related.

12.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see section 12.~~1~~2.2.2.~~2~~) and, if applicable, in the investigator's brochure as not requiring a notification without delay.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

12.2.2 Specific features of the protocol

12.2.2.1 Other events that require the investigator to notify the sponsor without delay

- Adverse events judged as being "medically significant"

    - Infectious complications grade III, according to GREFIG score
    - Absolute Neutrophil Count (ANC) < 500 on D28 post-transplantation

- Grade ≥ 2 acute GVHD according to the revised Magic consortium 2016 (Appendix 20.3) criteria
- Moderate or severe chronic GVHD

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- Information concerning the donor or the donation discovered by chance after the donation and whose consequences are likely to lead to a risk for the health of patients and recipients must be declared directly to the Agence de la Biomédecine in accordance with decree n°2016-1622 of the CSP and via the Agence de la Biomédecine's internal applications (Biovigie and Cristal donneur).
- Adverse events of particular interest

  Acute grade II-IV GVHD according to the Magic consortium 2016 (Appendix 20.3) classification or a moderate or severe chronic GVHD according to the NIH classification (Appendix 20.4)
  Secondary cancer
  According to last PRAC assessment report dated from 31 October 2019 (EMA/682560/2019) about Lemtrada® (alemtuzumab), the following adverse events schould be declared as adverse events of particular interest: myocardial ischaemia, myocardial infarction, haemorrhagic stroke, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage, thrombocytopenia, immune-mediated diseases such as autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH).

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

In addition, the adverse events of particular interest will be transmitted to the DSMB members by the sponsor (represented by its safety Department) without delay. These terms are described in the DSMB's charter.

- ***In utero*** exposure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.
If the drug is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor. The events are reported using a special form, appended to the protocol (cf. Appendix N°2).

- Exposure ***via*** **breastfeeding**

Exposure *via* breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational product.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure *via* breastfeeding.

- **Serious incident**

Any biovigilance incident must be reported to the local correspondent of biovigilance with the biovigilance form. The sponsor must be informed as soon as the investigator becomes aware of a serious incident.

12.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form e-CRF.

- *Normal and natural course of the condition*:

− *scheduled inpatient hospitalization for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]*

− *inpatient hospitalization for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition*

− *emergency inpatient hospitalization upon enrollment or prolongation of hospitalization upon enrollment for monitoring the condition under investigation*

● *Complication usually related to conditioning and transplantation:*

- Grade ≤ 1 GVHD according to the revised Magic consortium 2016 (Appendix 20.3) *criteria*

- Mild chronic GVHD (Appendix 20.4)

- Infection grade < 3 according to GREFIG score

- Absolute Neutrophil Count (ANC) ≤ grade3 according to CTCAE scale within 28 days post-transplantation

- Headache, loss of appetite, increase or temporary decrease of blood pressure

- Fever, pancytopenia, thrombopenia, anemia < grade 3 according to CTCAE scale.

● *Complication usually related to blood sample: pain, hematoma on puncture site, malaise.*

● *Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care*

The investigator must report these events to his *Centre Régional de Pharmacovigilance* (CRPV).

12.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject signs the consent form
- throughout the whole follow-up period intended by the trial
- indefinitely, if the SAE is likely to be due to the experimental product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

12.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's safety Department by e-mail (eig-vigilance.drc@aphp.fr) to the sponsor's safety department. It is possible to send the SAE to the Safety department by fax to the sponsor's safety department, fax No. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail and in order to avoid duplicates.

For trials which use e-CRF
- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by mail;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the "Follow-up form for reporting a pregnancy occurring in a clinical trial".
The investigator must monitor the pregnant woman until delivery or until premature interruption, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure as for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described in this section.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

12.2.5 Biovigilance reporting to the sponsor

12.2.5.1 Definitions

According to the article R. 1211-31 of the French Public Health Code [*Code de la Santé Publique]*, are defined:

- Incident: any accident or error originating from the procedures performed on the elements, products or derivatives mentioned in part I.1° of the article R1211-29, which causes or is likely to cause:
  a) An adverse effect in subjects mentioned in part I.3° of the article R. 1211-29;

b) The loss of the element, product or derivative
c) A quality or security defect of the element, product or derivative.

- Serious incident:
  a) Any adverse event which causes or is likely to cause:
     - A serious adverse effect or an unexpected adverse effect in persons mentioned in part I.3° of the article R.1211-29;
     - Any important loss of the element, product or derivative which prevents the graft transplant from being performed or the product from being administered;
  b) An abnormal increased rate of adverse events or unexpected adverse effects
  c) Any donor or graft's information that has been accidentally found out after the graft collection which is likely to impact patients and recipients' health

- Unexpected adverse effect: Any adverse effect (serious or not) for which the nature, severity or outcome is not expected according to criteria defined in article R. 1211-33, part 7° recognized by the Biomedicine Agency [*Agence de Biomédecine*] or with the health condition of the persons mentioned in article R. 1211-29, part 3°.

12.2.6 Role of the sponsor

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational product throughout the trial.

12.2.6.1 Analysis and declaration of serious adverse events occurring to the patients

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and study procedures (HSCT including reduced conditioning regimen and GVHD prophylaxis) and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational product are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ The serious adverse events associated with the study procedures are:

- For HSCT including reduced conditioning regimen (TBI and alemtuzumab) and GVHD prophylaxis (sirolimus):

− refer to the Investigator's Brochure in Appendix 20.10.

Some of the most common toxicities associated with the transplantation (including the reduced conditioning regimen and GVHD prophylaxis) are:

- Graft versus host disease according to the revised Magic consortium 2016 (Appendix 20.3) criteria
- Chronic GVHD according to the NIH classification (Appendix 20.4)
- Infection
- Fever, aplasia, pancytopenia, neutropenia, thrombopenia, anaemia
- Gastrointestinal: nausea, vomiting
- Neurological disorders: visual disorders

- Cardiovascular: arterial hypertension
- Miscellaneous: serum sickness (skin rashes, pain and swelling of the joints) and anaphylaxis (hypotension, difficulty breathing and severe hives, mucositis)

➢ For additional medicinal product (including anesthesia, hydroxyurea):

- Complications of the disease despite supportive care including hydroxyurea and transfusions programs. Chronic transfusions can lead iron overload and alloimmunization. Hydroxyurea can lead hypofertility.
- refer to the SmPC of for specialities of additional medicinal products.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

Specific rules for serious adverse events of special interest:
The sponsor may be required to declare serious adverse events of special interest, with the same procedures and within the same timelines as for SUSARs.

12.2.6.2 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational product, modifications in the investigational product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will report to the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe what urgent safety measures have been taken by the sponsor.

Following the initial declaration of any emerging safety issue, the sponsor will report to ANSM and the Ethics committee any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days upon knowledge of the sponsor.

If the suspected unexpected serious adverse reaction meets the definition of an emerging safety issue, the sponsor will report both the SUSAR and the emerging safety issue to the ANSM according to the appropriate modalities and within the regulatory timelines as previously described.

12.2.6.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse events that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The sponsor produce one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted to the competent authorities no later than 60 days after the date of the first participant inclusion in the clinical trial.

12.2.7 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority (ANSM) and to the Ethics committee.

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled. Then the DSMB will meet every 6 months and at the request of the sponsor if necessary. The DSMB’s preliminary meeting should take place before the protocol submission to competent health authority (ANSM) and Ethics committee.

The members of the DSMB are:

- Methodologist, Dr Cédric LAOUENAN Hôpital Bichat
  email cedric.laouenan@inserm.fr
- Hematologist, Pr Stéphanie N GUYEN. Hôpital Pitié Salpêtrière Paris
  email : stephanienguyenquoc@hotmail.com
- Hematologist, Pr Jean-Hugues DALLE,President of DSMB. Hôpital Robert Debré Paris
  email : jhugues.dalle@gmail.com
- Hematologist, Dr A. FERSTER, Responsable de l'unité Hémato-Oncologie, Immunologie et Transplantation, Hôpital Universitaire des Enfants Reine Fabiola (ULB) Avenue J.J. Crocq, 15, 1020 Bruxelles-Belgique
  email : alina.ferster@huderf.be

The DSMB's principle missions and their operating procedures are described in the DSMB chart of the clinical trial.
The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.

13 DATA MANAGEMENT

13.1 Right to access source data and documents

13.1.1 Data access

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the research and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

13.1.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the study. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for 15 years.

13.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the experimental product, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the Clinical Trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

13.2 Data processing and storage of research documents and data

13.2.1 Identification of the person responsible and the location for data processing

Pr. Sylvie CHEVRET from Service BioStatistique et Information Médicale (SBIM) Hôpital Saint Louis, AP-HP, Paris will be responsible for data entry and the relevant procedures. The same goes for conducting the statistical analysis.

13.2.2 Data entry

Data will be entered electronically via a web browser.

13.2.3 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

For France:

- Commitment to comply with "Reference Methodology" MR-001

This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology".

13.2.4 Archiving

All specific documents for a clinical trial on a investigational product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research.
This indexed archiving applies to:

- A sealed envelope for the investigator, containing one original of all information sheets and consent forms signed by all individuals at the site who participated in the research;
- A sealed envelope for the sponsor, containing one copy of all information sheets and consent forms signed by all individuals at the site who participated in the research;
- "Study" binders for the Investigator and the sponsor, containing (non-exhaustive list):
  - all successive versions of the protocol (identified by version no. and date), and its appendices
  - decisions of the CPP
  - correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - Final report
- The case report forms

13.3 Ownership of the data

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

14 STATISTICAL ASPECTS

The following analysis sets will be considered:

- Intent-to-treat: Includes all randomized subjects analyzed according to their planned group. This will refer to the primary analyses
- Per protocol set: Includes all subjects from the intent-to-treat set without any major violations which could affect the evaluation of the primary efficacy endpoint and analyzed according to their actually group. This will be used as secondary, exploratory or sensitivity analyses
- Safety set: Includes all subjects who take any amount of study drug.

14.1 Planned statistical methods

Quantitative data will be described as median and interquartile range, and qualitative data as count and percentage.

Statistical analyses will be perform on the intent-to-treat (ITT) population, meaning that all patients will be analyzed according to their planned group ("exposed" = HSCT or "non exposed" = standard of care), regardless of the fact that they were finally transplanted or not. No efficacy interim analysis will be performed, and the final analysis will take place two years after the last patient's inclusion.

Primary endpoint, 2-years event-free survival after time of inclusion, will be non-parametrically assessed using Kaplan Meier estimate, and will be compared between two arms using log-rank test. Effect of transplantation will be assessed by hazard ratio (HR) and its 95% confidence interval by fitting a Cox proportional hazards regression model.

Complementary to the primary analysis:

- a sensitivity analysis, based on the per protocol population
- a sensitivity analysis, based on propensity score matching analysis will be performed. This analysis seeks to ensure the robustness of the primary analysis by handling potential residual imbalances between arms in confounders. Propensity score will be constructed based on known or observed prognostic factors and known or observed factors associated with treatment arm.

Methods for analysing secondary endpoints:

- All time to event secondary endpoints will be analysed in the same way as the primary outcome
- Binary endpoints will be compared between two arms using Fisher's exact test
- Continuous endpoints will be compared between two arms using Wilcoxon rank sum test
- Endpoints with multiple measurement across follow-up will be analysed using mixed effect regression model to take into account the within-patients correlation

Statistical analysis for safety data:

Safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events reported, changes in vital signs and laboratory test results from baseline (Day 0 pre-dose) to specified time points throughout the study, and concomitant medications use. The population of analysis will be all patients included in the trial according to the treatment actually received, regardless of the duration.

Adverse Events

Adverse events reported during the study will be coded using a MedDRA dictionary. Incidence of treatment-emergent adverse events will be summarized by treatment group and the following:

- System organ class and preferred term
- System organ class, preferred term and severity

These summaries will be presented for the following subsets:

- Serious adverse events
- All adverse events
- Drug-related adverse events
- Adverse events resulting in discontinuation of study drug
- Outcome of adverse events
- Action taken

For tables reporting adverse events by severity, if a subject has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented.

A summary and by-subject listing will be provided for all subjects who experienced any adverse events, serious adverse events, or adverse events resulting in discontinuation of study drug.

A sequential analysis of tolerance data will be performed, using Bayesian methods, to allow detecting any increased rate of serious adverse events differing across arms. Using a Bayesian beta-binomial model, the rate of SAEs will be sequentially computed with its 95% credible interval in both arms. The maximum rate acceptable for SAEs has been set at 30%. The probability that the rate of SAEs is above 30% will be computed. Adverse events of special interest (AESI) defined above (section 12.1.2.2.1) and a tolerable risk difference of δ =20% between the two arms on the AESIs that involve both arms will be considered. Using a Bayesian beta-binomial model, the event rate of each AESIs in the two arms will be assessed for each DSMB and upon request of the DSI (along with their 95% credible interval). When SAEs and AESs involved both arms, the probability that the risk difference exceed δ, will be assessed for each DSMB and upon request of the DSI.

Method for taking into account missing, unused or invalid data

In case of missing data, complete case analyses will be performed. Confirmatory analyses will be performed by using multiple imputation by chained equation to impute outcome as well as missing characteristics. At least 20 imputed datasets will be considered.

14.2 Hypotheses for calculating the required number of subjects, and the result

Considering that 30% of patients will have a matched related donor, this study will need to enroll 26 patients in the transplant arm and 52 patients in the control arm, to demonstrate a 2-year EFS of 80% in the transplant arm versus 40% in the other arm, controlling for type I error of 5% and with a power of 80%, with a two-sided test.

14.3 State whether subjects who exit the study prematurely will be replaced and in what proportion

Only patients who exit the study between the time when eligibility criteria and the informed consent have been obtained and the time when results of HLA typing are available (i.e. before the group could be defined) will be replaced.

15 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored Clinical Trial.

15.1 General organization

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

15.1.1 Strategy for site opening

15.1.2 The strategy for opening the centres established for this study is determined using the appropriate monitoring plan. Data quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

15.2 Case report forms

The case report forms should only contain the data needed to analyse the study and publish the results. All other data needed to monitor the participants during and after the study are recorded in the medical file.
All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and must be written clearly and legibly. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.
Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data. In addition, there are consistency checks to ensure the data are verified immediately upon being entered.

The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The sponsor will keep the original. The investigator must keep a copy.

15.3 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

The sponsor has its own procedures for managing these non-compliances.

15.4 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.
The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

15.5 Principal Investigator's declaration of responsibility

Before starting the study, each investigator will give the sponsor’s representative a signed and dated copy of his/her most recent curriculum vitæ, produced within the past year, and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must describe any previous participation in clinical research and related training.

Each investigator will agree to comply with legislation and to conduct the study in line with regulations, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role and must supply their CV.

16 ETHICAL AND LEGAL CONSIDERATIONS

16.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L.1122-1-1 of the Code de la Santé Publique - CSP (French Public Health Code), no medical research can be carried out on a person without his/her free and informed consent, obtained expressly after the person has been given the information specified in Article L.1122-1 of said Code.

The person will be given the sufficient time between receiving the information and being asked to sign the consent form.

The person's free and informed written consent will be obtained by the principal investigator, a doctor representing the investigator or a qualified person, before the person is enrolled on the study.

The information sheet and one copy of the consent form, signed and dated by the research participant and by the investigator the doctor representing the investigator or a qualified person, will be sent to the individual prior to being enrolled on the study.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent [or the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP] as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Special rule: If the person is physically unable to give his or her written consent, consent may be obtained, in descending order of priority, from a legal representative, family member or a close relative. These persons must have no connection whatsoever to the investigator or the sponsor.

Information and consent of parents or legal guardians in the case of a study involving a minor

In accordance with Article L.1122-2 of the Code de la Santé Publique - CSP (French Public Health Code), when an interventional research study involves a non-emancipated minor, consent must be given by the legal guardians.
The guardians will be given sufficient time between receiving the information and being asked to sign the consent form.

The free and informed written consent of the legal guardians is obtained by the investigator, or by a doctor representing the investigator, before the minor is enrolled on the study [Before inclusion and signed consent].

Special rule: information and consent from the only parent or legal guardian present
If only one parent is present (DOM-TOM case), the investigator should arrange to discuss the study with the absent parent (telephone, skype or others) and to send consent forms for his/her signature. The absent parent may receive the forms by mail or fax, and may mail or fax a signed consent form back to the investigator. The child may not be enrolled until the absent parent has returned the signed consent form to the investigator.

However, in accordance with Article L1122-2 of the Code de la Santé Publique - CSP (French Public Health Code), consent may be given by the present legal guardian, subject to the following conditions:

- the study involves minimal risks - the minor is not taking part in the study as a healthy volunteer

- the other legal guardian is unable to give consent within a suitable deadline given the specific methodology of the study and its purpose.

Information for minors participating in the research
Minors will be given the information specified in Article L. 1122-1 of the Code de la Santé Publique - CSP (French Public Health Code), adapted to suit their level of understanding, by both the investigator and their legal guardians.
Minors will be asked to agree to take part in the human research study. In all cases, the investigator must accept a minor's refusal to participate or a withdrawal of their agreement.

One copy of the signed and dated consent form is given to the parents or legal guardians as well as to the investigator or the doctor representing the investigator. The investigator will retain the original. At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information recorded in the minor's medical file
The investigator will record the minor's participation in the clinical study in the minor's medical file, along with the procedure for informing and obtaining consent from the legal guardians and for informing the minor and a record of the minor's agreement to take part.

Special rule: minors who reach the age of majority whilst still participating in the study
Minors who reach the age of majority during their participation in the study will be given the relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

16.2 Prohibition of concomitant clinical studies participation and exclusion period after the study

Whilst participating on this research study, participants may not take part in any other clinical study without first speaking to the doctor in charge of this study.

16.3 Compensation for participants

There will be no compensation

16.4 Registration on a national register of clinical research participants

Registration on a national register of clinical research participants is not compulsory for research that does not involve a healthcare product. Nevertheless, the Ethical Review Board may decide to register participants.

16.5 Legal obligations

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Innovation Department (DRCI) in order to conduct the study in accordance with Article L.1121-1 of the Code de la Santé Publique - CSP (French Public Health Code). AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

16.6 Request for approval from the CPP

AP-HP, as sponsor, obtains prior approval from the CPP for its interventional research studies, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

16.7 Request for approval from the ANSM

AP-HP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of investigational products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

16.8 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with "Reference Methodology" MR-001

This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology"

16.9 Amendments to the research

Any substantial amendment made to the protocol must be sent to the sponsor for approval. Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented.
The information sheet and the consent form can be revised if necessary in particular if there is substantial amendment to the study or if adverse reactions occur.

16.10 Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority's guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

17 FUNDING AND INSURANCE

17.1 Sources of monetary support

The source of funding for the trial is a PHRC-N-17_0155 from French Ministry of Health.

17.2 Insurance

As per Article L.1121-10 of the Code de la Santé Publique - CSP (French Public Health Code), insurance policies must cover the third party liability of the sponsor and all study staff, and insure them against the financial consequences of any damage caused by the human research study.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participants and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique - CSP (French Public Health Code).

18 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and name the sponsor AH-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming the sponsor and financial backers).

18.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "AP-HP" first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

18.2 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2017 (Ministry of Health)"

This research program will be registered on the website http://clinicaltrials.gov/ under number : NCT04046705.

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20 LIST OF ADDENDA

20.1 Formulaire EIG

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur une préparation de thérapie cellulaire**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (4 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr). Il est à noter qu'il est possible de transmettre les EIG au secteur Vigilance par télécopie au 01 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi des EIG par mail (afin d'éviter les doublons).

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche	
Acronyme : **DREPA-RIC**	**Date de notification :** |__|__| |__|__| |2|0|__|__| (jj mm aaaa)
Code de la Recherche : K170912J	**Date de prise de connaissance de l'EIG par l'investigateur :** |__|__| |__|__| |2|0|__|__| (jj mm aaaa)
Risque : D	

Titre complet de la recherche : A prospective multicenter trial comparing allogeneic matched related hematopoietic stem cell transplantation after a reduced intensity conditioning regimen, with standard of care in adolescents and adults with severe sickle cell disease

2. Identification du centre investigateur

PARTIE RÉSERVÉE AU PROMOTEUR
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

Nom de l'établissement : .... Ville et code postal : .... Service :	Investigateur (nom/prénom) : .... Tél : .... Fax : .... E-mail : ....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
N° centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__|__|__|
mm aaaa

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |_2_|_0_|__|__|

Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
....
....
....
....
....
....
....

Greffe réalisée ☐ Oui ☐ Non

Date de la greffe : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ Groupe (HSCT) ☐ Groupe (standard)

4. Préparation de thérapie cellulaire - administré avant la survenue de l'évènement *(barrer l'encadré si traitement non débuté)*

Nom du produit expérimental (CSH, CSM, USP....)	Voie(1)	Nombre de cellules administrées / Dose	Heure de début	En cours(2)	Heure de fin
....	....	.........x 10^6/kg	|__||__| hh |__||__| min	☐	|__||__| hh |__||__| min
....	....	.........x 10^6/kg	|__||__| hh |__||__| min	☐	|__||__| hh |__||__| min

Acronyme : DREPA-RIC

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
N° centre - n° ordre de sélection - initiale nom - initiale prénom

5. Radiothérapie/médicaments de conditionnement/immunosuppresseurs/prophylaxie GVH administrés avant la survenue de l'évènement indésirable NA ☐

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie *(1)*	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours *(2)*	Date de fin *(jj/mm/aaaa)*
alemtuzumab :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
alemtuzumab :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
alemtuzumab :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
alemtuzumab :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
alemtuzumab :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
TBI		Gy	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
sirolimus :	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

PARTIE RÉSERVÉE AU PROMOTEUR REFERENCE VIGILANCE : Référence GED : REC-DTYP-0192

....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

6. Autres procédures de la recherche (préciser le nom de spécialité de préférence) *(ex. : Hydroxyurée, etc.) (barrer l'encadré si non applicable)*

						Chronologie	
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie (1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours (2)	Date de fin *(jj/mm/aaaa)*	Avant la survenue de l'EIG	Après la survenue de l'EIG
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
....	....		|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

7. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable *(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)*

➩ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie* *1 : arrêt* *2 : diminution de la posologie* *3 : augmentation de la posologie* *4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament* *1 : lié au médicament* *2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Acronyme : DREPA-RIC

Référence de la personne se prêtant à la recherche : |___|___|___| - |___|___|___|___| - |___| - |___|
N° centre - n° ordre de sélection - initiale nom - initiale prénom

8. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

....

....

....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels :

....

Organe(s) concerné(s) :

....

....

....

....

....

....

Date d'apparition de l'EIG :

|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

Délai entre la date de la dernière administration du produit ou la date de procédure ajouté par la recherche et la date de survenue de l'EIG :

|__||__|
jj

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

L'évènement fait-il suite à un incident lors de la collecte, fabrication, préparation, transformation, conservation, transport, distribution ou administration du produit expérimental ?

☐ Non ☐ Oui Date de l'incident : |__|__| |__|__| |_2_|_0_|__|__|

Si oui, joindre le certificat de libération du lot concerné ☐ Ci-joint

Correspondant Local de Biovigilance (CLB) informé : non ☐ oui ☐

Si oui, préciser le contact du CLB : .....

Cet incident a-t-il été déclaré : oui ☐ (joindre le formulaire de biovigilance) non ☐

Des <u>mesures symptomatiques</u> ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

Préciser : .....

L'évènement fait-il suite à :

- une erreur médicamenteuse ? ☐ Non ☐ Oui , préciser :..... Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ? ☐ Non ☐ Oui , préciser :..... Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ? ☐ Non ☐ Oui , préciser :..... Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) : ..... ☐ Non ☐ Oui , préciser :..... Date : |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
.....
.....

<u>Degré de sévérité</u> : ***(selon CTCAE) :***

☐ grade 1 ☐ grade 2 ☐ grade 3
☐ grade 4 ☐ grade 5

<u>Degré de sévérité de l'EIG</u> :

En cas d'infection, se référer au score de GREFIG :

Grade I ☐ Grade II ☐ Grade III ☐

En cas de GVH aiguë, se référer aux critères de la Magic Consortium 2016 :

Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐

En cas de GVH chronique, se référer à l'échelle NIH:

Préciser le **SCORE**:

.....

Evolution de l'événement

☐ **Décès** Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
○ sans relation avec l'EIG
○ en relation avec l'EIG

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :** Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
○ sans séquelles
○ avec séquelles, préciser lesquelles :
.....
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

9. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : ……
……
……

10. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés, notamment le compte-rendu d'hospitalisation, les résultats chimérisme….]……
……
……

11. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ Oui :

○ **à la préparation de thérapie cellulaire**

○ **au conditionnement de la greffe**

Préciser : ……

○ **Prophylaxie GVH (sirolimus)**

○ **Autres procédures de la recherche?**
La/lequel(le) : ……

☐ **Non :**
☐ **à la progression de la maladie faisant l'objet de la recherche : dépranocytose**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**
☐ **à une maladie intercurrente, laquelle : ……**
☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** *Référence GED : REC-DTYP-0185*

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

1. Identification de la recherche

Acronyme : **DREPA-RIC**
Code de la recherche : **K170912J**

Notification initiale ☐ Suivi de notification ☐ N° du suivi |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche : A prospective multicenter trial comparing allogeneic matched related hematopoietic stem cell transplantation after a reduced intensity conditioning regimen, with standard of care in adolescents and adults with severe sickle cell disease

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance : |__|__| |__|__| |__|__|__|__|
Date d'inclusion : |__|__| |__|__| |2|0|__|__|

☐ Groupe (HSCT) ☐ Groupe (standard)

Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance : |__|__| |__|__| |__|__|__|__|
Date d'inclusion : |__|__| |__|__| |2|0|__|__|

☐ Groupe (HSCT) ☐ Groupe (standard)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite
Autre (préciser) :				

4. Antécédents maternels

Médicaux :

Chirurgicaux :

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable*).

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		
	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche *(Barrez l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |2|0|__|__|		
	|__|__| |__|__| |2|0|__|__|		

Acronyme : DREPA-RIC

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0185

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	Investigateur	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification des cancers secondaires/myélodysplasies survenant au cours d'une recherche portant sur un Médicament ou produit assimilé**	PARTIE RESERVEE AU PROMOTEUR REFERENCE VIGILANCE : *Référence GED : REC-DTYP-0191*

Ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

Notification initiale ☐ Suivi d'EIG ☐ N° du suivi |__|__|

1. Identification de la recherche

Acronyme : **DREPA-RIC**

Code de la Recherche : **K170912J**

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche : A prospective multicenter trial comparing allogeneic matched related hematopoietic stem cell transplantation after a reduced intensity conditioning regimen, with standard of care in adolescents and adults with severe sickle cell disease

Risque : ☐ A ☐ B ☐ C ☒ D

Plan expérimental : ☐ Essai non comparatif ☒ Essai comparatif ☐ Double aveugle ☐ Simple aveugle ☒ Ouvert ☐ Randomisé ☐ Non randomisé

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....

Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__| (n°centre – n° ordre de sélection – initiale nom – initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__| |__|__|__|__| (jj mm aaaa)

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....

☐ Groupe (HSCT) ☐ Groupe (standard)

4. Diagnostic du cancer secondaire/de la myélodysplasie

4.1 Diagnostic clinique :

Date du diagnostic : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Confirmation histologique : ☐ Non ☐ Oui

Confirmation cytologique : ☐ Non ☐ Oui

Diagnostic final retenu : .....

4.2 Grade : (précisez l'échelle de classification ex : TNM) ☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV .....

4.3 Grade histologique ☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV

4.4 Si autre classification, précisez :

4.5 Antécédents médicaux pertinents : ☐ Non ☐ Oui, précisez :

5. Précision de l'imputabilité de l'investigateur

5.1 Selon l'investigateur, l'événement indésirable grave (cancer secondaire/myélodysplasie) est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :** ○ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : Le(s)quel(s) ?**

Lequel : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

Lequel : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

○ **à la (aux) procédure(s)/acte(s) de la recherche : La/le(s)quel(les) ?**

La/lequel(le) : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

La/lequel(le) : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

☐ **Non :** ○ **à la progression de la maladie faisant l'objet de la recherche** : (à compléter)

○ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....

○ **à une maladie intercurrente, laquelle :** .....

○ **autre, préciser :** .....

5.3 La survenue de cet EIG est-elle susceptible d'être liée à un manque d'efficacité du ME ? ☐ Non ☐ Oui

6. Détails de la chimiothérapie administrée pour traiter la pathologie initiale (phase)

☐ Induction |__|__| |__|__| |2|0|__|__| jj mm aaaa	☐ Consolidation |__|__| |__|__| |2|0|__|__| jj mm aaaa
☐ Post greffe : renseignez la partie 6.2	☐ Maintenance |__|__| |__|__| |2|0|__|__| jj mm aaaa
☐ Autre :	☐ Interphase

6.1 Médicament(s) ou produit(s) assimilé(s) de chimiothérapie anticancéreuse ou de thérapie ciblée avant la survenue du cancer secondaire/de la myélodysplasie *(barrez l'encadré si aucun traitement débuté)* :

Nom commercial ou Dénomination Commune International	Date de première administration Ou non administré	Date de dernière administration Ou en cours (2)	Voie d'administration(1)	Posologie / 24h	Lien de causalité avec l'EIG *(Relation selon méthode OMS)*
	|__|__| |__|__||2|0|__|__| jj mm aaaa ☐ Non administré	|__|__| |__|__||2|0|__|__| jj mm aaaa ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
	|__|__| |__|__||2|0|__|__| jj mm aaaa ☐ Non administré	|__|__| |__|__||2|0|__|__| jj mm aaaa ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

(1) Voie d'administration : VO=voie orale ; IM=intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)
(2) En cours au moment de la survenue de l'EIG

6.2 Greffe de cellules souches hématopoïétiques (CSH) pour le traitement de la pathologie initiale :

☐ Non ☐ Oui, précisez ci-dessous :

Date de la greffe : le |__|__| |__|__| |2|0|__|__| jj mm aaaa ☐ autogreffe ☐ allogreffe	Si allogreffe : Donneur : ☐ apparenté ☐ fichier volontaires / banque

Origine CSH : ☐ CSP ☐ Moelle osseuse ☐ Sang de cordon

Date de sortie d'aplasie : \|__\|__\| \|__\|__\| \|2\|0\|__\|__\| jj mm aaaa

6.3 Traitements de conditionnement de la greffe (immunosuppresseurs, irradiation corporelle, etc.) :

☐ Non applicable ☐ Applicable, précisez ci-dessous le schéma thérapeutique :

Nom commercial ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__||2|0|__|__|	|__|__| |__|__||2|0|__|__|		
	|__|__| |__|__||2|0|__|__|	|__|__| |__|__||2|0|__|__|		

7. Statut de la pathologie initiale à la date de survenue du cancer secondaire/de la myélodysplasie
(Joindre si possible les résultats du dernier myélogramme le cas échéant) :

☐ Rémission complète le |__|__| |__|__| |_2_|_0_|__|__|
☐ Rémission avec séquelles le |__|__| |__|__| |_2_|_0_|__|__|, précisez les séquelles :
☐ Rémission partielle le |__|__| |__|__| |_2_|_0_|__|__|, précisez :
☐ Stable depuis le |__|__| |__|__| |_2_|_0_|__|__|
☐ Maladie en progression
☐ Rechute depuis le |__|__| |__|__| |_2_|_0_|__|__|

8. Traitement du cancer secondaire/de la myélodysplasie

8.1 Hospitalisation(s) :

Hospitalisation (1) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|
Hospitalisation (2) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|
Hospitalisation (3) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|

8.2 Intervention chirurgicale : ☐ Non ☐ Oui, précisez ci-dessous :

Type d'intervention chirurgicale :	Date de l'intervention chirurgicale :
	|__|__| |__|__| |_2_|_0_|__|__|

8.3 Chimiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique, date(s) de début, les posologies et dates de fin si applicable :

8.4 Radiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique et les doses :	Date de début :	Date de fin :
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|

8.5 Traitement(s) adjuvant(s) : ☐ Non ☐ Oui, précisez ci-dessous :

8.6 Une greffe de CSH a été réalisée pour le traitement du cancer secondaire/de la myélodysplasie : ☐ Non ☐ Oui, précisez ci-dessous :

Date de la greffe : le |__|__| |__|__| |_2_|_0_|__|__| ☐ autogreffe ☐ allogreffe	Si allogreffe : Donneur : ☐ apparenté ☐ fichier volontaires / banque

Origine CSH : ☐ CSP ☐ Moelle osseuse ☐ Sang de cordon

Date de sortie d'aplasie : |__|__| |__|__| |_2_|_0_|__|__|

9. Evolution du cancer secondaire/de la myélodysplasie

9.1 Etat actuel (hors décès)

☐ Rémission complète le |__|__| |__|__| |_2_|_0_|__|__|
☐ Rémission avec séquelles le |__|__| |__|__| |_2_|_0_|__|__|, précisez les séquelles :
☐ Rémission partielle le |__|__| |__|__| |_2_|_0_|__|__|, précisez :
☐ Stable depuis le |__|__| |__|__| |_2_|_0_|__|__|
☐ Maladie en progression
☐ Rechute depuis le |__|__| |__|__| |_2_|_0_|__|__|

9.2 Evolution fatale

Date du décès : |__|__| |__|__| |_2_|_0_|__|__|

Autopsie effectuée : ☐ Non ☐ Oui (joindre le compte-rendu)

Veuillez spécifier la « cause du décès » rapportée dans le certificat de décès / le rapport d'autopsie :

Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	

20.2 Questionnaire: MOS-SF 36

Nom :	Étiquettes du patient
Prénom :	
Date de naissance :	
Service :	
Hôpital/Centre MPR :	
Examinateur :	
Date du jour :	

Medical Outcome Study Short Form-36 (MOS SF-36)

Ces items peuvent être regroupés en trois catégories :

Le statut fonctionnel

Il comprend 10 items sur l'activité physique (PF), 2 items sur la vie et relations avec les autres (SF), 4 items sur les limitations dues à l'état physique (RP) et 3 items sur les limitations dues à l'état psychique (RE).

Le bien-être

Il comprend 5 items sur l'évaluation de la santé psychique (MH), 4 items sur l'énergie et la vitalité (VT) et 2 items sur les douleurs physiques (BP).

L'évaluation globale de la santé

Elle est fondée sur 5 items de perception globale de l'état de santé (GH) et un item servant à décrire les modifications de l'état de santé au cours de l'année écoulée (HT).

D'autres domaines pouvant être pertinents n'ont pas été choisis dans la SF 36 : sexualité, sommeil, situation et positionnement familial (family function).
Dans deux dimensions, la réponse se fait de manière binaire (oui/non) et dans les six autres de manière qualitative ordinale (3 à 6 réponses possibles). Pour chaque dimension, les scores aux différents items sont codés puis additionnés et transformés linéairement sur une échelle allant de 0 à 100. Un score résumé physique (physical composite score : PCS) et un score résumé psychique (mental composite score : MCS) peuvent être calculés selon un algorithme établi. Dans la langue anglaise, différentes versions ont été proposées : la version standard, la version aiguë et la version utilisée en Grande Bretagne. À noter que la version aiguë de la SF 36 utilise la notion d'une semaine au lieu de quatre semaines utilisées dans la version standard. Cette version est plus intéressante lorsque le questionnaire est administré hebdomadairement ou bi-mensuellement. Malgré différentes traductions en français réalisées par des équipes canadienne et suisse, une adaptation française a été proposée par Leplège, afin d'améliorer la fiabilité de la SF 36 dans la population hexagonale.

Comment répondre au questionnaire :

Les questions qui suivent portent sur votre état de santé, telle que vous la ressentez.
Ces informations nous permettront de mieux savoir comment vous vous sentez dans votre vie de tous les jours.
Veuillez répondre à toutes les questions en entourant le chiffre correspondant à la réponse choisie, comme il est indiqué. Si vous ne savez pas très bien comment répondre, choisissez la réponse la plus proche de votre situation.

1 / 5

1/ Dans l'ensemble, pensez-vous que votre santé est :

1 : excellente.
2 : très bonne.
3 : bonne.
4 : médiocre.
5 : mauvaise.

2/ Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé actuel ?

1 : bien meilleur que l'an dernier.
2 : plutôt meilleur.
3 : a peu près pareil.
4 : plutôt moins bon.
5 : beaucoup moins bon.

3/ Voici la liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours.
Pour chacune d'entre elles, indiquez si vous êtes limité en raison de votre état de santé actuel :

Listes d'activités	OUI beaucoup limité(e)	OUI peu limité(e)	NON pas du tout limité(e)
A Efforts physiques importants tels que courir, soulever un objet lourd, faire du sport…	1	2	3
B Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	1	2	3
C Soulever et porter les courses	1	2	3
D Monter plusieurs étages par l'escalier	1	2	3
E Monter un étage par l'escalier	1	2	3
F Se pencher en avant, se mettre à genoux, s'accroupir	1	2	3
G Marcher plus d'un kilomètre à pied	1	2	3
H Marcher plusieurs centaines de mètres	1	2	3
I Marcher une centaine de mètres	1	2	3
J Prendre un bain, une douche ou s'habiller	1	2	3

4/ Au cours de ces quatre dernières semaines,
et en raison de votre état physique

	OUI	NON
A Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles ?	1	2
B Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
C Avez-vous dû arrêter de faire certaines choses ?	1	2
D Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire)	1	2

5/ Au cours de ces quatre dernières semaines,
et en raison de votre état émotionnel
[comme vous sentir triste, nerveux(se) ou déprimé(e)]

	OUI	NON
A Avez-vous réduit le temps passé à votre travail ou activités habituelles ?	1	2
B Avez-vous accompli moins de choses que vous ne l'auriez souhaité ?	1	2
C Avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention que d'habitude ?	1	2

6/ Au cours de ces quatre dernières semaines,
dans quelle mesure votre état de santé, physique
ou émotionnel vous a-t-il gêné(e) dans votre vie sociale
et vos relations avec les autres, votre famille, vos amis
ou vos connaissances ?

1 : pas du tout.
2 : un petit peu.
3 : moyennement.
4 : beaucoup.
5 : énormément.

1 : nulle. 2 : très faible. 3 : faible.
4 : moyenne. 5 : grande. 6 : très grande.

8/ Au cours de ces quatre dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques ?

1 : pas du tout. 2 : un petit peu. 3 : moyennement.
4 : beaucoup. 5 : énormément.

9/ Les questions qui suivent portent sur comment vous vous êtes senti(e) au cours de ces quatre dernières semaines. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée.
Au cours de ces quatre dernières semaines y a-t-il eu des moments où :

	En permanence	Très souvent	Souvent	Quelquefois	Rarement	Jamais
A Vous vous êtes senti(e) dynamique ?	1	2	3	4	5	6
B Vous vous êtes senti(e) très nerveux(se) ?	1	2	3	4	5	6
C Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remontez le moral ?	1	2	3	4	5	6
D Vous vous êtes senti(e) calme et détendu(e) ?	1	2	3	4	5	6
E Vous vous êtes senti(e) débordant d'énergie ?	1	2	3	4	5	6
F Vous vous êtes senti(e) triste et abattu(e) ?	1	2	3	4	5	6
G Vous vous êtes senti(e) épuisé(e) ?	1	2	3	4	5	6
H Vous vous êtes senti(e) heureux(se) ?	1	2	3	4	5	6
I Vous vous êtes senti(e) fatigué(e) ?	1	2	3	4	5	6

10/Au cours de ces quatre dernières semaines, y a-t-il eu des moments où votre état de santé, physique ou émotionnant vous a gêné(e) dans votre vie et vos relations avec les autres, votre famille et vos connaissances ?

1 : en permanence.
2 : une bonne partie du temps.
3 : de temps en temps.
4 : rarement.
5 : jamais.

11/Indiquez pour chacune des phrases suivantes dans quelle mesure elles sont vraies ou fausses dans votre cas :

	Totalement vrai	Plutôt vrai	Je ne sais pas	Plutôt fausse	Totalement fausse
A Je tombe malade plus facilement que les autres	1	2	3	4	5
B Je me porte aussi bien que n'importe qui	1	2	3	4	5
C Je m'attends à ce que ma santé se dégrade	1	2	3	4	5
D Je suis en excellente santé	1	2	3	4	5

20.3 Questionnaire HADS

Le questionnaire HADS (de l'anglais *Hospital Anxiety and Depression Scale*)

Dans la série de questions ci-dessous, cochez la réponse qui exprime le mieux ce que vous avez éprouvé au cours de la semaine qui vient de s'écouler. Ne vous attardez pas sur la réponse à faire : votre réaction immédiate à chaque question fournira probablement une meilleure indication de ce que vous éprouvez, qu'une réponse longuement méditée.

Score	Anxiété	Score	Dépression
	Je me sens tendu ou énervé :		Je prends plaisir aux mêmes choses qu'autrefois
3	❒ la plupart du temps	0	❒ oui, tout autant
2	❒ souvent	1	❒ pas autant
1	❒ de temps en temps	2	❒ un peu seulement
0	❒ jamais	3	❒ presque plus
	J'ai une sensation de peur comme si quelque chose d'horrible allait m'arriver		Je ris facilement et vois le bon côté des choses
3	❒ oui, très nettement	0	❒ autant que par le passé
2	❒ oui, mais ce n'est pas grave	1	❒ plus autant qu'avant
1	❒ un peu, mais cela ne m'inquiète pas	2	❒ vraiment moins qu'avant
0	❒ pas du tout	3	❒ plus du tout
	Je me fais du souci :		Je suis de bonne humeur :
3	❒ très souvent	3	❒ jamais
2	❒ assez souvent	2	❒ rarement
1	❒ occasionnellement	1	❒ assez souvent
0	❒ très occasionnellement	0	❒ la plupart du temps
	Je peux rester tranquillement assis à ne rien faire et me sentir décontracté :		J'ai l'impression de fonctionner au ralenti :
0	❒ oui, quoi qu'il arrive	3	❒ presque toujours
1	❒ oui, en général	2	❒ très souvent
2	❒ rarement	1	❒ parfois
3	❒ jamais	0	❒ jamais
	J'éprouve des sensations de peur et j'ai l'estomac noué :		Je ne m'intéresse plus à mon apparence :
0	❒ jamais	3	❒ plus du tout
1	❒ parfois	2	❒ je n'y accorde pas autant d'attention que je le devrais
2	❒ assez souvent		❒ il se peut que je n'y fasse plus autant attention
3	❒ très souvent	1	❒ j'y prête autant d'attention que par le passé
		0	
	J'ai la bougeotte et n'arrive pas à tenir en place :		Je me réjouis d'avance à l'idée de faire certaines choses :
	❒ oui, c'est tout à fait le cas		❒ autant qu'auparavant
3	❒ un peu	0	❒ un peu moins qu'avant
2	❒ pas tellement	1	❒ bien moins qu'avant
1	❒ pas du tout	2	❒ presque jamais
0		3	
	J'éprouve des sensations soudaines de panique :		Je peux prendre plaisir à un bon livre ou à une bonne émission radio ou de télévision :
	❒ vraiment très souvent		
3	❒ assez souvent	0	❒ souvent
2	❒ pas très souvent	1	❒ parfois
1	❒ jamais	2	❒ rarement
0		3	❒ très rarement
	☜ **Total du score pour l'anxiété**		☜ **Total du score pour la dépression**

Chaque réponse correspond à un chiffre. En additionnant ces chiffres, on obtient un score total par colonne (anxiété et dépression). Si le score d'une colonne est supérieur ou égal à 11, cela signifie que vous souffrez d'anxiété ou de dépression (selon la colonne concernée).

20.4 Classification de la GVH aigue (MAGIC CONSORTIUM 2016)

Reference: Harris et al. Biology of Blood and Marrow Transplantation 2016; 22 (1): 4-10

20.4.1 Stade par organe

Stade	Peau	Foie (bilirubine)	Tube digestif haut	Tube digestif bas (quantification des selles/jour)
0	Absence d'érythème cutané actif	< 2 mg/dl	Absence ou présence de manière intermittente de nausée, vomissement ou anorexie	< 500 ml/jour ou<3 selles/jour
1	Erythème maculopapulaire <25% SC	2–3 mg/dl	Présence de manière persistante de nausée, vomissement ou anorexie	500–999 ml/jour ou 3–4 selles/jour
2	Erythème maculopapulaire 25 – 50% SC	3.1–6 mg/dl	-	1000–1500 ml/jour ou 5–7 selles/jour
3	Erythème maculopapulaire > 50% SC	6.1–15 mg/dl	-	>1500 ml/jour Ou >7 selles/jour
4	Erythème généralisé (>50% SC) avec décollement (bulles) et desquamation > 5% SC	>15 mg/dl	-	Douleur abdominale importante avec ou sans ileus ou hémorragie digestive indépendamment du volume de selles

SC=surface corporelle

20.4.2 Grade global de GVH aigue (en fonction du stade par organe le plus sévèrement atteint)

- Grade 0: Pas de stade 1-4 dans aucun des organes
- Grade I: Stade 1–2 cutané sans atteinte hépatique, ni digestive haute et basse
- **Grade II: Stade 3 cutané et/ou stade 1 hépatique et/ou stade 1 digestif haut ou bas**
- Grade III: Stade 2–3 hépatique et/ou stade 2–3 digestif bas + stade 0-3 cutané et/ou stade 0-1 digestif haut
- Grade IV: Stade 4 cutané, hépatique ou digestif bas avec stade 0-1 digestif haut

20.5 Cotation de la GVH chronique

Manifestation de GVHD chronique

Dans le cas de manifestations cliniques parallèles comme un épisode infectieux ou une réaction médicamenteuse, cette évaluation ne sera pas prise en compte.

Un Karnofsky < 60% avec une perte de poids > 15% et des infections récurrentes sont en général des signes de GVHD chronique extensive.

Manifestation de GVHD chronique

Les anomalies cliniques selon les organes touchés permettant d'évaluer la GVHD chronique sont les suivantes :

Peau Erythème, sécheresse, prurit, changement de pigmentation (vitiligo, hyperpigmentation) plaques papulosquameuses, nodules, exfoliation, rash maculo-papulaire ou urticaire, sclérodermie, morphée (une ou plusieurs lésions lisses indurées et circonscrites)

Ongles Onychodystrophie, onycholyse, striés, fendus.

Cheveux Canitie prématurée (cuir chevelu, cils, sourcils), alopécie, amincissement du cuir chevelu, raréfaction de la pilosité corporelle.

Bouche Sécheresse, brûlures, gingivite, mucite, atrophie gingivale, érythème, lichen, ulcères, atrophie labiale, changement de pigmentation, contracture de la bouche, caries dentaires.

Yeux Sécheresse, brûlures, photophobie, douleur, larmoiement, sensation de grain de sable

Organes Sécheresse, sténose vaginale, dyspareunie, érythème vulvaire, atrophie **génitaux** génitale, lichen

Foie Élévation du bilan hépatique sanguin sans autre cause connue. En l'absence d'une autre atteinte organique, une biopsie est nécessaire pour confirmer le diagnostic.

Poumons Bronchiolite oblitérante, toux, sifflements, dyspnée d'effort, bronchites chroniques ou sinusites.

Tube digestif Anorexie, nausées, vomissements, perte de poids, diarrhées, dysphagie, malabsorption.

Fasciite Ankylose et réduction des mouvements, avec occasionnellement gonflement, douleurs, crampes, érythème et induration, atteignant le plus fréquemment les avant- bras les poignets et les mains, les chevilles, les jambes et les pieds, incapacité d'étendre les poignets sans fléchir les doigts ou les coudes, contractures.

Muscles Faiblesse proximale, crampes.

Squelette Arthralgies proximales des articulations des os du bassin, et parfois d'articulation moins importantes

Séreuses Douleurs pulmonaires ou cardiaques secondaires à une pleurésie ou une péricardite.

20.6 Gradation de GVHD chronique par organe

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS† FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Gradation de la GVH chronique globale (selon Filipovitch et al. BBMT 2005)

Affected organ	Mild	Moderate					Severe		
Number of organ affected	1 or 2 without significant dysfunction	≥3	or	≥ 1	**or**	lung	≥ 1	or	lung
Score of the achievement of each organ	1 (except lung)	1	or	2		1	3		≥2

20.7 Treatments contraindicated or not recommended in patients with G6PD deficiency

ansm
Agence nationale de sécurité du médicament et des produits de santé

Liste des substances actives (classées par ordre alphabétique) des médicaments pouvant provoquer un accident hémolytique chez les personnes atteintes de déficit en G6PD

Les médicaments contre-indiqués

Les médicaments déconseillés

Les médicaments qui peuvent être utilisés, sous réserve que la posologie soit strictement respectée

Acide acétylsalicylique (Aspirine)	😐
Acide ascorbique (Vitamine C)	😐
Acide nalidixique[§]	⊗
Acide pipémidique	☹
Antipyrine (voir Phénazone)	☹
Aspirine (voir Acide acétylsalicylique)	😐
Bleu de méthylène (voie injectable)*	⊗
Carbutamide[§]	☹
Chloroquine	☹
Ciprofloxacine	☹
Dapsone	⊗
Dimercaprol	☹
Enoxacine	☹
Flumequine	☹
Glibenclamide	☹
Glibornuride[§§]	☹
Gliclazide	☹
Glimépiride	☹
Glipizide	☹
Hydroxychloroquine	☹
Lévofloxacine	☹
Lomefloxacine	☹
Métamizole sodique (voir Noramidopyrine)[§§]	⊗
Moxifloxacine	☹
Nitrofurantoïne	⊗
Noramidopyrine (Métamizole sodique)[§§]	⊗
Norfloxacine (voie orale)	☹
Ofloxacine (voies orale et injectable)	☹
Paracétamol	😐
Péfloxacine	☹
Phénazone (voies cutanée et nasale)	☹
Phytoménadione (voir Vitamine K)	☹
Prilocaine	☹
Primaquine*	⊗
Quinine	☹
Rasburicase	⊗
Spiramycine	☹
Streptokinase*	☹
Sulfacétamide[§§]	☹
Sulfadiazine (voie orale)	⊗
Sulfadiazine (voie cutanée)	☹
Sulfadoxine	☹
Sulfafurazole	⊗
Sulfaguanidine[§]	⊗
Sulfaméthizol	☹
Sulfaméthoxazole	⊗
Sulfasalazine	⊗
Triméthoprime	⊗
Vitamine C (voir Acide ascorbique)	😐
Vitamine K_3 (Phytoménadione)	☹

* *Substances actives qui ne figuraient pas dans la liste de 2008*
[§] *Substances actives non disponibles sur le marché français*
[§§] *Substances actives non disponibles sur le marché français et sans autorisation de mise sur le marché en France*

Liste mise à jour en décembre 2013 / Pour plus d'informations : ansm.sante.fr/g6pd

20.8 Nouvelles informations sur la sécurité de l'alemtuzumab (EMA/220110/2019 « Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing » et des recommandations du PRAC du 31/10/2019 :

Lemtrada | European Medicines Agency (europa.eu)
Lemtrada, INN-alemtuzumab (europa.eu)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2019
EMA/682560/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1483/C/3718/0028

Lemtrada

INN/active substance: alemtuzumab

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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[…]

20.9 Questionnaire : Consommation orale d'opioïdes

1/ Durant le dernier mois, avez-vous consommé des opioïdes par voie orale : exemple

- Codéine : codoliprane, Codafalgan, Dafalgan ou Efferagan codéiné, Klipal codeiné
- Tramadol, Contramal, Topalgic, Ixprim…
- Morphine par voie orale : Actiskenan, skenan, oramorph, moscotin, oxycodone, oxynormoro,
- Fentanyl…)

□ OUI □ NON

2/ Si OUI,

Quel type ? (Plusieurs réponses possible)

□ Codéine (Codoliprane, Codafalgan, Dafalgan ou Efferagan codéiné, Klipal codeiné…)

□ Tramadol, Contramal, Topalgic, Ixprim…

□ Morphine par voie orale : Actiskenan, skenan, oramorph, moscotin, oxycodone, oxynormoro

□ Autres : préciser : …….

3/ Si OUI,

Evaluer votre consommation sur le dernier mois d'opioïdes per os :

□ 1 à 7 jours sur le mois

□ 7 à 14 jours sur le mois

□ 15 à 21 jours sur le mois

□ pratiquement quotidienne

20.10 Investigator's Brochure

See in attached documents entitled : 2018-A01454-51_BI_VX.0_year/month/day_DREPA-RIC with the corresponding version of the document.