Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study
"HaploRescue"

INTERVENTIONAL RESEARCH PROTOCOL

Version N°1.0 of 03/08/2020
Project code number: Pxxxxxx/EUDRACT No.:

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INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

Research code number:

Title: Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study “HaploRescue”

Version N° 1.0 of: 03/08/2020

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:
Pr Régis Peffault de Latour Date: ……/……/……..
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1 SUMMARY

Full title	Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study
Acronym	HaploRescue
Coordinating Investigator	Pr Régis Peffault de Latour
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Prognosis of patients with graft failure is dismal, and re-transplantation is the sole option for long-term survival. Currently, there is no consensus concerning therapeutic options in patients with primary or secondary (within the 60 days post-transplantation) graft failure and finding a new donor within an acceptable delay is challenging. Literature is poor on the subject while the overall survival of such patients is about 30% at 1 year (1, 2). This situation thus represents today a very challenging unmet medical need. Recently, haploidentical (haplo) related donor Stem Cell Transplantation (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil (3). Our group re-transplanted a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT from her son using PTCy (5). We then retrospectively collected and analyzed data from 26 primary graft failure patients transplanted between 2011 and 2017 in 15 centers on behalf of French Society for Stem Cell Transplantation and Cell Therapy (SFGM-TC). The study population consisted mainly of patients with primary or secondary (within the 60 days post-transplantation) graft failure who underwent haplo-SCT and received PTCy as graft-versus-host-disease prophylaxis. The 1-year overall survival was about 60% suggesting that this approach might be a valid option in this particular poor clinical situation but now need validation through a phase II multicenter, national, prospective cohort study (4).
Main objective and primary endpoint	**Main objective**: To rescue patients with graft failure after a first allogeneic SCT (allo-SCT) using haplo-SCT with PTCy **Primary endpoint**: Overall Survival rate compared to an historical controls of 30% at 1 year.

Secondary objectives and endpoints	**Secondary objectives:** - Graft failure, GvHD, progression free survival, relapse, non-relapse mortality - Interval between first allo-SCT and rescue haplo-SCT - Quality of life - Chimerism - Immune reconstitution **Secondary Endpoints:** -Graft failure incidence. -Neutrophils and platelets engraftment at day 100 (3 consecutive days with neutrophiles >0.5 G/L and 7 consecutive days with platelets >20 G/L). Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions. The use of growth factors for poor hematopoietic reconstitution -Acute GvHD incidence at month 3 (M3) (date and maximum grading, first line treatment, response to steroids, treatment courses in case of steroid refractory GvHD. -Chronic GvHD incidence (date and grading at M24). -Relapse incidence at M12 and M24 -Progression free survival at M12 and M24 -Incidence of CMV and EBV infection at M12 -Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24 -Non-relapse mortality M3, M6, M12 and M24 -Incidence of cardiac toxicities at M3 -Overall survival at M24 -Interval between first allo-SCT and rescue haplo-SCT -Quality of life questionnaire (EORTC QLQ-C30- v3) at inclusion, post-transplantation, M3, M12, M24 -Chimerism at , M3, M12 -Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M1, M3, M6, M12 and M24 post-transplantation
Design of the trial	Phase II multicenter, national, prospective cohort study
Population of trial subjects	Patients over 3 years old and all hematological diseases suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allogeneic hematopoietic stem cell transplantation (allo-SCT)
Inclusion criteria	**Patients:** -Aged from 3 years and older -All hematological diseases -Suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allo-SCT -With usual criteria for allo-SCT: • ECOG ≤ 2 • No severe and uncontrolled infection • Cardiac function compatible with high dose of cyclophosphamide

	• Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine clearance >30ml / min -With identification of a haploidentical donor (brother, sister, parents, adult children or cousin) -Absence of donor specific antibody (DSA) detected in the patient with a MFI ≥ 2000 (antibodies directed towards the distinct haplotype between donor and recipient) - With health insurance coverage (bénéficiaire ou ayant droit). - Understand informed consent or optimal treatment and follow-up. - Contraception methods must be prescribed during all the duration of the research. Women and men of childbearing age must use contraceptive methods within 12 months and 6 months after the last dose of cyclophosphamide, respectively. -Having signed a written informed consent (2 parents for patients aged less than 18)
Exclusion criteria	**Patients:** - Aged< 3 years old - With uncontrolled infection - With Seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCV and associated hepatic cytolysis - Yellow fever vaccine within 2 months before transplantation - Cancer in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix) - Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50% - Heart failure according to NYHA (II or more) - Preexisting acute hemorrhagic cystitis - Renal failure with creatinine clearance ≤ 30ml / min - Urinary tract obstruction - Pregnant (β-HCG positive) or breast-feeding - Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up - Tutorship or curatorship - Contraindications to treatments used during the research

Transplant modalities Medical product provided by the Sponsor	**Conditioning regimen** Fludarabine (30mg/m2/day from day -6 to day -4), Cyclophosphamide (14.5 mg/kg/day at day -6 and day -5) except for patients who received a total dose of Cyclophosphamide >100mg/Kg during the first Bone Marrow Transplantation Total Body Irradiation (2 Gray on day -1). **Source of stem cell source** Peripheral blood stem cell Minimal target dose of 4.10^6 CD34+ cells/kg of recipient **GvHD prophylaxis** Cyclophosphamide 50 mg/Kg/day at D+3 and D+4 Ciclosporine from day+5 (residual 200 à 300ng/l) Mycophenolate mofetyl at 15mg/Kg x2/day from day+5 **Prevention of EBV reactivation** Rituximab : 150mg/m2 at Day+5 post Haplo-SCT
Risks added by the trial	Risks are related to the SCT itself. In the haplo donor arm, cardiac toxicities and hemorrhagic cystitis will be particularly monitored.
Scope of the trial	Primary or secondary (within the 60 days post-transplantation) graft failure is a rare but devastating condition after SCT. A recent strategy for haplo related donor transplantation, which has had some success, is transplantation of T-cell replete grafts with intensive immune suppression. Few retrospective non-controlled registry studies recently suggest that outcomes after haplo-SCT using PTCy approach might be superior to actual standard of care (i.e. retransplantation from an unrelated donor). Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients. This study might thus favor this strategy in case of primary or secondary (within the 60 days post-transplantation) graft failure after 1st SCT.
Number of subjects included	For an objective of 31 patients to be allo-grafted, we anticipate 35 patients to include.
Number of sites	37 centres in France 2 centres in Belgium (affiliated to SFGM-TC) 1 centre in Switzerland (affiliated to SFGM-TC)
Duration of the trial	Inclusion period: 36 months Participation period : 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.9 patient/centre (0,02 patient/month/centre)
Statistical analysis	Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals. Comparaison with the historical controls of 30% at 1 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011. Terminal analysis will be performed after the follow-up of the last included patient.
Sources of funding for the trial	*PHRC-K 2019*

Trial will have a Data Monitoring Committee	*Yes*

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Hypothesis for the study

Prognosis of patients with graft failure is dismal, and re-transplantation is the sole option for long-term survival. Currently, there is no consensus concerning therapeutic options in patients with primary or secondary (within the 60 days post-transplantation) graft failure and finding a new donor within an acceptable delay is challenging. Literature is poor on the subject while the overall survival of such patients is about 30% at 1 year (1, 2). This situation thus represents today a very challenging unmet medical need.
Recently, haploidentical (haplo) related donor Stem Cell Transplantation (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil (3). Our group re-transplanted a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT from her son using PTCy (4). We then retrospectively collected and analyzed data from 26 primary graft failure patients transplanted between 2011 and 2017 in 15 centers on behalf of French Society for Stem Cell Transplantation and Cell Therapy (SFGM-TC). The study population consisted mainly of patients with primary or secondary (within the 60 days post-transplantation) graft failure who underwent haplo-SCT and received PTCy as graft-versus-host-disease prophylaxis. The 1-year overall survival was about 60% suggesting that this approach might be a valid option in this particular poor clinical situation but now need validation through a phase II multicenter, national, prospective cohort study (5).

2.2 Existing knowledge relating to the condition under investigation

Primary or secondary (within the 60 days post-transplantation) graft failure is a rare but devastating condition after SCT. A recent strategy of haplo related donor transplantation with T-cell replete grafts and intensive immune suppression showed very encouraging results in this situation (4, 5). Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients (all biologic parents and children of a patient are haplo and each sibling has a 50% chance of being haplo). This study might thus offer a real curative strategy in this particular dramatic clinical situation.

2.3 Summary of relevant pre-clinical and clinical trials

Currently, there is no consensus concerning therapeutic options in patients with graft failure, and finding a new donor within an acceptable delay may be challenging. Cord blood, unrelated donors, or haploidentical transplantation are alternatives. However, the literature is scarce on the subject, and the long-term overall survival (OS) of retransplanted patients is estimated to be about 30% (1)

In the past years haploidentical transplantations with post- transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis have shown promising results in the treatment of many hematologic diseases, including some cases of graft failure (6)

In this context, we analysed data from 24 patients with graft failure or loss retransplanted with a haploidentical donor who received post-transplant cyclophosphamide (PTCy) as graft-versus-host disease prophylaxis (GVHD) (4). Fludarabine-based reduced-intensity conditioning was used in 23 patients and the Baltimore regimen in 14 patients. The median delay between previous and salvage transplantation for graft failure was 63 days (range, 39 to 98). In addition to PTCy, all patients received cyclosporine, and 22 patients also received mycophenolate mofetil for GVHD prophylaxis. With a median follow- up of 353 days (range, 16 to 2010), 1-year overall survival (OS) was 56% (95% confidence interval, 38% to 81%). Transplant complications accounted for 80% of deaths. The cumulative incidence of neutrophil engraftment at day +30 was 79%. Cumulative incidence of grades II to IV acute GVHD at day 100 was 14%, and 1-year cumulative incidence of chronic GVHD was 31%. One-year cumulative incidence of relapse was 13%. Stem cell source did not impact on engraftment, GVHD, relapse, or OS. Salvage haploidentical transplant with PTCy for rescuing graft failure patients leads to an acceptable 1-year OS and might be a valid option in this poor situation and justified to validate this therapeutic option through the actual phase 2 protocol “HaploRescue”.

2.4 Description of the population of trial subjects and justification for the choice of subjects

All hematological diseases will be concerned by this research. Indeed, the approach for patients with malignant or non malignant diseases is exactly the same in term of strategy for second HSCT in case of graft failure.

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

The Baltimore group developed the PTCy strategy using haploidentical related donors with intra-venous injection at day +3 and day +4, using T-replete bone marrow in patients with advanced hematological malignancies (the so-called Baltimore protocole, reference 3). PTCy administered early at a fixed time point after bone marrow infusion, has shown to eradicate alloreactive donor and host T-cells, activated by respective antigens, thereby reducing the incidence of GVHD reaction (7). Details are indicated in section V.6.2 (“Transplant modalities”). We used this approach for a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT (5). The SFGM-TC retrospective study recently published was also using the Baltimore strategy (4). The difference with the Baltimore protocole is the choice to use Peripheral Blood Stem Cells (PBSC) as source of stem cells and not Bone Marrow (BM) to improve engraftment in this particular situation of graft failure and because more recent literature showed no difference in term os outcomes using PBSC or BM in the context of a Baltimore approach (section 6.2 “Transplant modalities”). The other difference is the introduction of Rituximab 150mg/m2 at Day+5 post HSCT to prevent the EBV reactivation (8). Indeed, EBV post transplant lymphoproliferative disorders (PTLD) is classical after alternative BMT. In a recent study using Cord Blood in patients with refractory aplastic anemia, the use of an early unique anti-CD20 injection (at day +5) was able to avoid EBV-associated lymphoproliferative disorder following BMT (9), illustrating the efficacy of an early anti-CD20 injection. EBV DNA monitoring, with early preemptive use of anti-CD20 in patients with increasing viral load will also help to prevent this type of complication (10).

2.6 Summary of the known and foreseeable benefits and risks for the study participants

Benefits will be evaluated in terms of efficacy to demonstrate a benefit in term of Overall survival at one year using haplo-SCT with PTCy for rescuing patients with graft failure.

Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients.
Risks are related to SCT itself. It is classical to estimate a higher risk of infections during second BMT because of intense immunosuppressive status. Patients will receive primary bacterial, viral and fungal prophylaxis to avoid as much as possible this risk.
PTCy will also be strictly followed in Haplorescue due to the known cardiac toxicity of cyclophosphamide and hemorrhagic cystits related to its use in this situation. To avoid any excess of toxicity, we also decided not to use Cyclophosphamide in the conditioning regimen, for patients who received a total dose of Cyclophosphamide >100mg/Kg during the first Bone Marrow Transplantation.

3 OBJECTIVES

3.1 Primary objective

The main objective is to demonstrate a benefit in term of Overall Survival (OS) at one year using haplo-SCT with PTCy for rescuing patients with graft failure.

3.2 Secondary clinical and biological objectives

- Graft failure, GvHD, progression free survival, relapse, non-relapse mortality, OS
- Interval between first allo-SCT and rescue haplo-SCT
- Quality of life
- Chimerism
- Immune reconstitution

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

Primary endpoint

Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals (CI). Comparaison with the historical controls of 30% at 1 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011 (11).

Secondary endpoints

- Graft failure incidence.
- Neutrophils and platelets engraftment at day 100 (3 consecutive days with neutrophiles >0.5 G/L and 7 consecutive days with platelets >20 G/L). Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions. The use of growth factors for poor hematopoietic reconstitution
- Acute GvHD incidence at M3 (date and maximum grading, first line treatment, response to steroids, treatment courses in case of steroid refractory GvHD.
- Chronic GvHD incidence (date and grading at M24).
- Relapse incidence at M12 and M24
- Progression free survival at M12 and M24
- Incidence of CMV and EBV infection at M12
- Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24
- Non-relapse mortality M3, M6, M12 and M24
- Incidence of cardiac toxicities at M3
- Overall survival at M24

- Interval between first allo-SCT and rescue haplo-SCT
- Quality of life questionnaire (EORTC QLQ-C30- v3) at inclusion, post-transplantation, M3, M6, M12, M24
- Chimerism at, M3, M12,
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M1, M3, M6, M12 and M24 post-transplantation
- Iron overload estimation at M1, M3, M6, M12 and M24

4.2 Research methodology

Design of the trial

Phase II multicenter, 3 countries, prospective cohort study. 31 patients will receive a haplo-SCT.

Number of participating sites

This is a multi-center study in 3 countries (France, Belgium and Switzerland) including most adult and paediatric transplant centres of the SFGM-TC (40 centres). Patients will be recruited in the hematology units and referred to the transplant team for the pre-transplant assessment.

Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection 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 trial.

4.3 Screening visit

The screening visit will take place within the 45 days prior to second haplo-SCT. The investigator will check the eligibility criteria and will propose the study to the patient. The transplant physician in charge of the patient will deliver informations about the protocol. Triplicated information and consent forms will be given to the patient by the investigator.
No additional test or specific examinations are performed for research. The patient assessment is performed in the usual care of haplo-SCT.

	Who informs the individual and collects their consent	**When is the individual informed**	**When is the individual's consent collected**
Patient or 2 parents for patients aged less than 18 years The “Non opposition” of the minor patient should be sought as soon as the minor is of age to understand	The transplant physician (investigator of research)	Screening visit	At the inclusion visit

4.4 Baseline visit

At this visit, the consent of the patient will be collected at the latest by D-10 before haplo-SCT. A Patient Information Sheet and consent form are given to the patient by the investigator; the investigator, and the third copy by the sponsor keep the original.
Baseline visit also consists in physical examination, biological testing and imagery. This assessment is performed according to the practice of the investigator. The donor's agreement is verified.

- **Physical examination**

- Reports of patient and disease history
- ECOG assessment
- Sorror score of comorbidities
- Complete physical examination with evaluation of tumor localization
-Electrocardiogram
- Echocardiogram with evaluation of left ventricular ejection
- Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking).
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)"
- Liver ultrasound and doppler echography (baseline values)

- **Biological tests**

- Complete Blood count
- Prothrombin time (PT), Partial thromboplastin time (PTT)
- ABO and Rh typing Blood cell
- Chemistry panel (serum electrolytes with creatinine, calcium, glucose, uric acid, magnesium levels, ferritin, CRP)
- Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine)
- Circulating protein electrophoresis
- Pregnancy test (for women of childbearing age)
- HLA compatibility check between recipient and donor
- Search of anti-HLA antibodies with LUMINEX technology (DSA)
- Chimerism markers' identification

- **Infectious assessment**

- Urine culture
- Viral serologies: Serology for hepatitis B and C, Aspergillus antigen, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV (2 Elisa tests), HTLV-1 and 2, toxoplasmosis (IgG and M), TPHA and VDRL

- **Tumor assessment**:

Pre-transplant disease evaluation
- Sinus and thorax CT scan

- **Imaging**

- Dental radiography
- Total body CT scan

- **Quality of life** (EORTC QLQ-C30- v3)

4.5 Follow-up visits

Post- transplant monitoring

Patients are monitored daily during initial hospitalization to detect possible complications of procedure or GvHD occurrence. Once patients get out from the hospital, the follow-up will be done according to each center policy and protocol requirement but at least once a week until Months 3 and then in consultation on a regular basis lifelong. The daily monitoring includes:

- Physical examination of the patient and safety assessment by collection of all adverse events/serious adverse events likely to occur as well as all actions taken because of these AEs. These AEs will be grading according to the CTC-AE scale.
- Complete Blood count, chemistry assessment with kidney and liver test will be performed
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 will be performed weekly (or according to clinical context)
- Grading of acute GvHD will be performed weekly during hospitalization and at each visit until J120
- Cardiologic monitoring: Electrocardiogram will be checked before the infusion of cyclophosphamide and repeated in association to a dosage of troponine and proBNP on a daily basis for 3 consecutive days after the administration of cyclophosphamide and repeated after if any doublt. Weight measure will be done twice a day to identify quickly cardiac problems during 3 weeks then once a day until J120. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide (JACIE procedure).

All adverse events (AEs) will be recorded. All AEs (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale. Acute GvHD shall be graded according to MAGIC CONSORTIUM 2016 (weekly during hospitalization and up to D120).

- Quality of life

<u>Follow-up visits M1, M2, M3, M6, M12, M24.</u>

- Clinical examination, blood cell count, chemistry panel with creatinine and liver test will be performed at each visit (routine follow-up).
- Disease evaluation will be performed at M3, M12, M24
- CD3/CD4/CD3/CD8/B lymphocytes/NK cells, protein electrophoreris and ferritin levels at M1, M3, M6, M12 and M24
- Chimerism at M3, M12,
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 ans toxoplasmosis at M1, M2, M3, M12.
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)“at J100
- Cardiac monitoring: a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M3, M12 and M24
- Safety assessment by collection of all adverse events/serious adverse events at each visit.
- Chronic GvHD and acute GvHD shall be graded as previously described.
- Quality of life at M3, M12, M24.

4.6 End of study visit

4.7 Expected length of participation, chronology and duration of the study.

Maximum period between screening and enrolment	45 days
Length of Inclusion period	36 mois
Duration of participation for each subject	24 months
Total study duration:	62 months

4.8 Table or diagram summarising the chronology of the study

	Screening	*Inclusion (baseline visit)*	*D0 = graft*	*Immediate post graft monitoring daily*	*M1*	*M2*	*M3*	*M6*	*M12*	*M24*
Patient (and or parents for minor) Information:	*x*									
Signature of the consent form (“non opposition” of the minor patient should be sought)		*x*								
Inclusion exclusion criteria check	*x*	*X*								
βHCG test (before start transplant modalitiest)		*x*								
Sorror comorbidities score		*X*								
Physical examination		*X*	*X*	*x*	*X*	*X*	*X*	*x*	*X*	*x*
Disease evaluation		*x*					*x*		*X*	
Pre-transplant evaluation		*X*								
Lung function test		*x*					*X*			
Cardiac monitoring (a)		*x*		*x (β)*						
Blood cell count		*x*	*X*	*x*	*x*	*x*	*x*	*x*	*X*	*x*
Chemistry panel with creatinine, liver test		*x*	*X*	*x*	*x*	*x*	*x*	*X*	*X*	*x*
(c) Aspergillus antigen, PCR for CMV, EBV, adenovirus, HHV-6			*X*	*X*	*x*	*x*	*x*	*x*	*x*	
Chimerism (b)		*X*					*x*		*X*	
Grading of acute GvHD				*X*	*x*	*x*	*x*			
CD3/CD4/ CD8/ / B lymphocytes (CD19) and NK cells(CD56), and protide electropheris ferritin level		*X*			*x*		*x*	*x*	*X*	*x*
Quality of life questionnaire (EORTC QLQ-C30-V3)		*X*		*Post graft*			*x*		*x*	*x*
Adverse events/serious adverse event *All toxicity not attributed to GvHD will be classified according to CTC-AE toxicity, v5.0*			*X*	*X*	*X*	*X*	*X*	*x*	*X*	*x*

(a) Cardiologic monitoring : Electrocardiogram and echocardiography at baseline visit for all the patient ,(β) : Only for haplo SCT group : Electrocardiogram will be checked before the infusion of cyclophosphamide and repeated in association to a dosage of troponine and proBNP on a daily basis for 3 cnsecutive days after the administration of cyclophosphamide. Weight measure will be done twice a day to identify quickly cardiac problems during 3 weeks then once a day until J120. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide. For all patients, a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M3, M12 and M24.
(b) On total blood. CD3+ specific chimerism might be of interest in case of total blood mixt chimerism (according to local policy)
(c) Weekly : Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6

4.9 Distinction between standard care and research

TABLE: "Standard care" vs. "added interventions" required specifically for the study

Procedures and treatments to be provided during the study	**Procedures and treatments associated with standard of care**	**Procedures and treatments added for the study**
Procedure/Treatments	Haploidentical SCT, conditioning regimen, GVHD and Infection prophylaxis, HSCT overall follow-up Injection of donor lymphocyte (DLI) in case of relapse	Rituximab 150mg/m2 at Day+5 post HSCT
Hospitalizations-Consultations		No
Imaging	Dental radiography Total Body CT scan	No

4.10 Termination and exit rules

Criteria and procedures for prematurely terminating the study treatment

4.10.1 Different situations

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

The investigator must:

- Document the reason(s)
- Schedule further follow-up visits, especially in case of a serious adverse event.

4.10.2 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.

➔Subject lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead

If a subject 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 subject exited the study:
- ☐ Explicit withdrawal of consent
- ☐ Death
- ☐ Subject's personal reasons
- ☐ Lost to follow-up

Monitoring subjects after the premature termination of study

If a subject exits the trial before the end of study, this will in no way affect the standard care received for his/her condition.

Full or partial cancellation of the study

AH-HP (the sponsor) or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Monitoring Committee in the following situations:
- 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 procedure, in light of which the objectives of the study or clinical programme 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.

In all the case, the participating subjects will be followed-up according to the usual practice of each centre.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients:
- Aged from 3 years and older
- All hematological diseases
- Suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allo-SCT
- With usual criteria for allo-SCT:
    - ECOG ≤ 2
    - No severe and uncontrolled infection
    - Cardiac function compatible with high dose of cyclophosphamide
    - Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine clearance >30ml / min
- With identification of a haploidentical donor (brother, sister, parents, adult children or cousin).
- Absence of donor specific antibody (DSA) detected in the patient with a MFI ≥ 2000 (antibodies directed towards the distinct haplotype between donor and recipient).

- With health insurance coverage (bénéficiaire ou ayant droit).
- Understand informed consent or optimal treatment and follow-up.
- Contraception methods must be prescribed during all the duration of the research. Women and men of childbearing age must use contraceptive methods within 12 months and 6 months after the last dose of cyclophosphamide, respectively.
- Having signed a written informed consent (2 parents for patients aged less than 18).

5.2 Exclusion criteria

Patients:
- Aged < 3 years
- With uncontrolled infection
- With seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCV and associated hepatic cytolysis
- Yellow fever vaccine within 2 months before transplantation
- Cancer in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix)
- Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50%
- Heart failure according to NYHA (II or more)
- Preexisting acute hemorrhagic cystitis
- Renal failure with creatinine clearance $\leq$ 30ml / min
- Urinary tract obstruction
- Pregnant (β-HCG positive) or breast-feeding
- Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up
- Tutorship or curatorship
- Contraindications to treatments used during the research (see SmPC)*

* Available on “Base de données publique des médicaments" website (http://base-donnees-publique.medicaments.gouv.fr/)

5.3 Clinical selection and Inclusion criteria of a donor

Clinical selection of donors must comply with the criteria defined by the decision of 04 November 2014 “fixant les modalités de sélection clinique des donneurs d’organes de tissus et de cellules”

- Intrafamilial donor having 1 HLA haplotype in common with the recipient
- Aged 18 to 60 years old). If no adult fulfills inclusion criteria, a minor donor may be chosen. In that case, the management of minor donors ≤ 18 years old will be done by a pediatrician, including the bone marrow harvest, and minor donors will give their assessment as the donor’s legally authorized representative in accordance with applicable laws and regulations and shall be documented.
- Presence of the usual clinical and biological criteria of eligibility of the donors of hematopoietic stem, including in particular the serological assessment authorizing the transplant. The management of the donor, before, during, and after the procedure, shall be done by a physician who is not in charge of the recipient. The follow-up of donors includes routine management and the management of collection-associated adverse events.
- No contraindication to administration of G-CSF

The modalities for mobilizing and collection of PBSC will be done according to JACIE accreditation.

5.4 Exclusion criteria of a donor

- Presence of donor specific antibody (DSA) with a MFI ≥ 2000 detected in the patient
- Pregnancy in the donor

5.5 Recruitment methods

The protocol is carried out by the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) (adult and pediatric centres). All members of SFGM-TC accepted to participate to this research (37 French sites and 2 in Belgium (Bruxelles and Liège) and 1 in Switzerland (Geneve).

	Number of subjects
Total number of subjects to be included	35 (31 allografts)
Number of sites	40
Enrolment period (months)	24
Number of subjects/site	0.9
Number of subjects/site/month	0.02

In France, between 2014 and 2017, 134 patients received a second HSCT because of graft failure with 25 pediatric patients.

6 TRANSPLANT PROCEDURE

6.1 Donor selection

The algorithm for the selection of a haploidentical donor has been define by the french society for stem cell transplantation (12, 13, 14).

6.2 Transplant modalities

Before to start treatments, a βHCG test will be done. Transplantation modalities are following European guidelines (15).

Conditioning regimen

The conditioning regimen will be uniform in all patients, mainly immunosuppressive and not myeloablative since graft failure is characterized by hypocellular bone marrow and no need for anti-tumoral effect. It will consist of Fludarabine (30 mg/m²/day from day -6 to day -4), pre-transplant cyclophosphamide (14.5 mg/kg/day at day -6 and day -5) except for patients who received a total dose of Cyclophosphamide >100mg/kg during the first Bone Marrow Transplantation, and Total Body Irradiation (2 Gray on day -1).

Stem cell source

The stem cell source will be peripheral blood stem cell (PBSC), known to improve engraftment in this particular situation of high risk of rejection (16). This will allow achieving a high dose of infused CD34+ cells, correlated with better engraftment in patients with graft failure (17). Moreover, good results have been reported using PBSC instead of bone marrow in the context of bone marrow failure (18), a similar situation to graft failure.
G-CSF mobilized PBSC will thus be used. The donor will receive G-CSF from day-4 to day-1 subcutaneously (10µg/kg/day), with the minimal target dose of 4.10^6 CD34+ cells/kg.

GVHD prophylaxis

- Cyclophosphamide 50 mg/kg/day at D+3 and D+4. The injection of cyclophosphamide will be accompanied by systematic injection of Mesna (Uromitexan®, 50 mg/kg) for the prevention of urinary toxicity. The dose of Mesna is twice that of cyclophosphamide divided in 4 injections per day of 30 minutes each. The first injection of Mesna is performed at the time of cyclophosphamide injection and then 3 hours, 6 hours and 9 hours after. Patients must not receive any immunosuppressive agents between the graft infusion and until day +5.

- Ciclosporine and Mycophenolate mofetil (MMF) from day+5

- Ciclosporine

3 mg/kg IV at D+5 (residual 200 à 300 ng/l) to start 24 hours after the last dose of cyclophosphamide
Ciclosporine will be injected intravenously over 24 hours or twice daily. When the oral route is possible, the treatment will be taken twice daily.
Ciclosporine is adapted to the renal function.
It is planned to stop the treatment:
- before J180 after a progressive withdrawal starting by 3 months post-SCT
- in case of renal failure (<30 ml/min) or thrombotic microangiopathy

- MMF at 15mg/kg x2/day IV or orally from day+5, to start 24 hours after the last dose of cyclophosphamide.

In absence of GvHD, MMF will be stopped between D35 and D45.
MMF will be stopped or decreased faster in case of unexpected prolonged cytopenias and in case of digestive disorders (diarrhea).

Prevention of EBV reactivation

All patients will receive 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m2) at Day+5 to prevent EBV reactivation.
Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before administration of Rituximab.

Infection Prophylaxis

Prophylactic and curative anti-infectious treatments (antibiotics, antivirals, antifungals) will be administered according to the ECIL recommendations (lwww.kobe.fr/ecil workshops, recommendations).

- Prevention of fungal infection by azols according to ECIL5, adapted to the SCT risk group (https://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx)
- Prevention of HHSV and VZV reactivation: aciclovir 250mg/m² x3/day IV then valaciclovir: 500 mg/day po.
- Prevention of toxoplasmosis reactivations and pneumocystis: Bactrim® 800 mg x3/week or atovaquone 750 mg x 2/day in case of cytopenias after engraftment

- Prevention of encapsulated bacteria: Oracilline® 50 000 UI/kg x 2/day
- Monthly polyvalent immunoglobulins if hypogammaglobulinemia (<4 g/L)

❖ Management of toxicities:

Antibiotics (aminosides, vancomycine), antivirals (Foscavir®), and antifungals (Ambisome®) will be adapted to the renal function. Voriconazole and posaconazole will be adapted to the hepatic function, Cymevan® to cytopenias. These adaptations will be regularly carried out in the transplantation department.

7 TREATMENT ADDED TO STUDY PARTICIPANTS

7.1 Additional medicinal products to transplant procedure

Rituximab

One injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m²) at Day+5. Rituximab will be provided by the sponsor.

Traceability information and monitoring compliance for the Rituximab

The DEC AGEPS ensures that the commercial boxes are cross-labelled with the regulatory indications for clinical trials and that the PUI are supplied to the investigation centres. A drug circuit will describe the packaging of treatments, the supply, modalities to administration, dispensing and destruction modalities at the level of each site. The treatment will be dispensed by the PUI upon presentation of a specific nominative prescription for the research.

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

The investigator should be verified that patients should not have a contraindication of treatments use in the study.

Authorized treatments

Anti-infectious treatments (antibiotics, antivirals, antifungals), transfusions, growth factors according to usual practice of each centres are authorized.

Treatments forbidden

Yellow fever vaccine is contraindicated.

Treatments not recommended

- For cyclophosphamide
- Attenuated vaccine
- Phenytoin
- For Fludarabine
- Pentostatine
- Dipyridamole or other inhibitor of adenoside captation

Patients receiving, Benzodiazepines, Carbamazepine, Corticosteroids, Chloral hydrate, Phenobarbital Rifampicin, should be closely monitored for signs of toxicity

With the exception of the drugs listed above, the other drugs will be administered according to the usual practice of the centre and at the discretion of the investigator.

7.3 Management of relapse

Management of relapse is at the discretion of the investigator. However, if the injection of donor lymphocyte (DLI) is envisaged, the following procedures will be recommended: start with a dose of $1x10^6$ CD3/kg, increasing by 0.5 log every 6 to 8 weeks up to $1x10^8$ CD3/kg in the absence of GVH (according to the recommendations of the SFGM-TC).

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

Progression-free survival

Progression-free survival (PFS) is defined as the time from graft until the occurrence of the following events: relapse (cytological) and death from any cause whichever comes first right.

Acute GvHD

Acute GvHD is defined according to MAGIC CONSORTIUM 2016 criteria (19). Each organ is rated with the diagnosis in stage, which define a grade. Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the period and maximum grade date. Histological documentation is recommended for GI GVHD.

Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 (20). The diagnosis of chronic GVHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:
A- Classical chronic GvHD in patients with only evidence of chronic GvHD
B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD
C- Late acute GvHD, which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

The severity of chronic GvHD is defined by the number of affected organs.

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		2		1	3		≥2

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

The parameters for assessing efficacy were collected according to the schedule in table paragraph 4.8.

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific steering Committee

1. Members of the committee: Pr Régis Peffault de Latour, Pr Sylvie Chevret, Pr Matthieu Resche Rigon, and for DRCD : Project manager and Clinical Research Assistant.
2. Missions:

The scientific steering committee will define the general organization and the conduct of the research. He will determine the initial methodology and oversee the trial.
He will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority

9.2 Data Safety Monitoring Board (DSMB)

See paragraph 10.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

Regarding this research, biovigilance applies for the donor. The vigilance of clinical trials applies.

10.1 Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints

The safety assessment shall be done by collecting all adverse events that occur during the research. All adverse event (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale (v5.0). Acute GvHD shall be graded according to MAGIC CONSORTIUM 2016 classification.

Adverse events shall be collected according to the schedule in table of paragraph 4.8 of the protocol.

10.2 Recording and reporting adverse events

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 to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal 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 to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

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

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal 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 medicinal 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 medicinal 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 medicinal 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 medicinal 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.

<u>Role of the investigator</u>

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:

- CTA-AE Toxicity Grading Scale, v5.0
- MAGIC CONSORTIUM 2016 classification for acute GvHD

The investigator must assess the **causal relationship** between the serious adverse events and the study procedures.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.2.1.1 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 10.2.1.2.2.) and, if applicable, in the investigator's brochure as not requiring a notification without any 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

10.2.1.2 Specific features of the protocol

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

- Adverse events judged as being **"medically significant"** (i.e. considered as "serious")
  - Non-engraftment
  - Bacterial, fungal viral and opportunist infectious complications (grade 3-4)
  - Veno-occlusive disease (moderate to severe)
  - Severe Thrombotic Microangiopathy
  - Idiopathic pneumonia (all stages)
  - Bronchiolitis obliterans (all stages)
  - Severe neurological disorders (coma, convulsion, encephalitis) occurring the first month post SCT
  - Cardiac toxicities (all stages) occurring in the first month post SCT
  - Overdose report
  - Infusion reactions, infections (grade 3-4) and heart-related problems related to cyclophosphamide
  - Severe dyspnoea, bronchospasm or hypoxia related to rituximab
  - Secondary neoplasia (excepted basal cell carcinoma of the skin or "in situ" carcinoma of the cervix).

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

- **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 investigational medicinal product 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.

10.2.1.2.2 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. A CRF extraction of these serious adverse events will be performed for the DSMB meeting.

- ***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
  - Worsening of the condition under investigation
  - In case of disturbance of biological values corresponding to an adverse event of grade ≤ 3 and no other symptoms (fever, etc.) associated with this adverse event, this event will not be declared to the promoter as a serious adverse event but only in the case report form.

- ***Special circumstances***
  - Hospitalization for a pre-existing illness or condition

- Transfer to the emergency ward with self-limiting event or judged as not serious by the investigator.

- ***Serious adverse events during the trial possibly related to the graft procedure realized as part of the patient's standard care (anti-infectious prophylaxis).***

The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (ANSM), etc.

10.2.1.3 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 begins treatment for the allograft
- throughout the whole follow-up period intended by the trial
- indefinitely, if the SAE is likely to be due to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities).

10.2.1.4 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 (de-identified). 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 email;

- 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 initial notification and follow-up report forms for pregnancy exposure during trial participation.
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, 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 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 above.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

Role of the sponsor

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

10.2.1.5 Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and study procedures
- All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal 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, is considered unexpected.
  The sponsor, acting through its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

- For serious adverse events likely to be related and considered expected to study procedures:
  - refer to the Investigator's Brochure and to the SmPC for fludarabin, cyclophosphamide, uromitexan, ciclosporin, mycophenolate mofetil, rituximab and drugs used for premedication (reference to latest version available on http://base-donnees-publique.medicaments.gouv.fr).

- Reporting to the competent authority

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.

Note: the sponsor will report to the Agence de la Biomédecine (French health competent authority for biovigilance) and to the ANSM the unexpected adverse effects occurring in the donor and serious incidents without delay as soon as the sponsor becomes aware.
As a reminder, regarding this research, biovigilance applies for the donor. For patients treated in both groups, the vigilance of clinical trials applies.

Any suspected unexpected serious adverse reaction related to a drug must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

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

10.2.1.6 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 medicinal product, modifications in the investigational medicinal 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 inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

10.2.1.7 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of inclusion of first patient.

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. 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:
Pr André Tichelli (Bâle, Suisse), Pr Jakob Passweg (Bâle,Suisse) and Dr Raphaël Porcher (Hôtel-Dieu hospital, Paris). 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.

11 DATA MANAGEMENT

Data collection

11.1 Identification of data recorded directly in the CRFs which will be considered as source data

11.2 Right to access source data and documents

11.2.1.1 Access to data

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 clinical trial 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 (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2.1.2 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 trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

11.2.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.

Under no circumstances will the names and addresses of the subjects be shown.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

Identification of the data processing manager and the location(s)

The management and processing of the data will be done by the Centre de traitement de données INCA de l'APHP, Service de Diostatistique et Information Médicale (sDBIM), hôpital saint Louis, Paris (Pr. Sylvie Chevret).

Data entry

Data will be entered electronically via a web browser for all 3 countries.

Data processing (CNIL, the French Data Protection Authority) in France

This trial is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

All personal data for this trial will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

11.4 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.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

The analysis will be based on the intent-to-treat basis, that is, including all randomized patients whatever they were administered the treatment under study or not. Only patient consent withdrawals with positive report of not using their data, if any, will be excluded.
A secondary pre-treated analysis will be done.
One interim analysis will be performed at mid-inclusion, while the terminal analysis will be done once the required number of events (n=146) will be observed.

Baseline summary statistics, namely percentages or median [interquartile range, IQR], will be computed in each randomized arm, without any statistical test of comparison.

The right censored endpoint will be estimated using nonparametric methods. Kaplan Meier curves and cumulative incidence curves will be considered in case of non informative or informative censoring with comparison across randomized arms based on the log-rank test or the Gray test, respectively. Adjustment on potential confounders will used the Cox proportional hazards models.

Statistical analyses will be performed on SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.

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

A two-sided, one-sample logrank test calculated from a sample of 31 subjects achieves 90,3% power at a 0,05 significance level to detect a proportion surviving of 0,55 in the new group when the proportion surviving in the historic control group is 0,30. These proportions surviving are for a period of 12,0. Subjects are accrued for a period of 36,0. Follow-up continues for a period of 12,0 after the last subject is added. The probability that a subject experiences an event during the study is 0,74. The expected number of events during the study is 23. It is assumed that the survival time distributions of both groups are approximated reasonable well by the Weibull distribution with a shape parameter of 1,00 (21).

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

The analysis will be based on the intent-to-treat basis, that is, including all patients included and having received at least the conditioning for their graft. Only patient consent withdrawals with positive report of not using their data, if any, will be excluded.

12.4 Anticipated level of statistical significance

All tests will be two-sided with a type I error rate fixed at 0.05.

12.5 Statistical criteria for termination of the study.

Terminal analysis will be performed after the follow-up of the last included patient.

12.6 Method for taking into account missing, unused or invalid data

All the efforts will be done to avoid missing data in the outcomes.
Missing values for the main outcome measure are not expected to be observed; nevertheless, in case of occurrence, they will be handled using time-to-event methods in which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study using competing-risks estimates.
Missing values for predictors will be imputed using multiple imputation techniques based on chained equation, unless the rate of missing data is low, below 5% (in which case, only simple imputation based on the median value will be used).
All outliers will be checked carefully

12.7 Management of modifications made to the analysis plan for the initial strategy.

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the data base.
All modifications to the original protocol will be described in the SAP.

13 QUALITY CONTROL AND ASSURANCE

Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their 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 research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan. In practice, the centres will be opened with a priority for the centres that will have an eligible patient or within 3 months of the start of the research.

Scope of site monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level High.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with Good Clinical Practice as well as with 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 by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: 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

13.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. 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 entered. 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 study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 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, good clinical practice 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.

13.5 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 and inspections. These audits and inspections cannot be refused on the basis 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 trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

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.

13.6 Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor’s representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

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

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person’s role and will provide their CVs.

13.7 Pharmacist's declaration of responsibility

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of 15 days is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

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.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Information of the holders of parental authority and their consent in the case of a study protocol involving a minor
In accordance with Article L.1122-2 of the Code de la santé publique (French Public Health Code), when an interventional study involving human participants is conducted on a non-emancipated minor, consent must be given by the holders of parental authority.

A reflection period of 15 days is given to those with parental authority between the time when they are informed and when they sign the consent form.

The freely-given written informed consent of the holders of parental authority is obtained by the investigator, or by a physician representing the investigator, before definitive inclusion of the minor in the study.

Information for minors participating in the research

Minors receive the information specified in Article L. 1122-1 of the *Code de la Santé Publique* (French Public Health Code), appropriate to their level of understanding, both from the investigator and from the holders of parental authority.

Minor's personal endorsement is sought regarding their participation in the study involving human participants. In any cases, the investigator cannot override their refusal or the revocation of their acceptance.

One copy of the signed and dated consent form is given to the holders of parental authority. The principal investigator or a physician representing him/her will keep one copy.
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 holders of parental authority as well as the procedure for informing the minor and a record of the minor's non-rejection to take part.

Special circumstances: the minor reaches the age of majority during his or her participation in the study

Minors who reach the age of majority during their participation in the study will be given new, relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

14.2 Prohibition of concomitant clinical studies participation and exclusion period after the trial, if applicable

No exclusion period of participation after the participant has finished this study is defined in the context of this research.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies or in minimal risk and constraint study that does not involve therapeutic strategies, but this should be reported to the physician who follows it in the present research.

14.3 Legal obligations

The sponsor's role

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Development Department (DRCD) in order to conduct the study in accordance with Article L.1121-1 of the 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.

Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional s Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

Request for approval from the ANSM

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

Declaration of compliance with the MR 001 "Reference Method" [include if applicable]

AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
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.

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.

Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for *30 years* after the end of the trial.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the site who participated in the study for the investigator;
- One copy of all the information sheets and signed consent forms signed for all individuals at the site who participated in the study for the sponsor;
- "Study" binders for the Investigator and the sponsor, containing:
  - all successive versions of the protocol (identified by version no. and date), and its appendices
  - the ANSM authorisations and CPP decisions
  - correspondence
  - the enrolment list or register
  - the appendices specific to the study
  - the final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC-K 2019 (French Ministry of Health)".

15.2 Insurance

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 participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. 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-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION

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

16.1 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 trial is funded by an internal call for tenders at the AP-HP, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and 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

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

16.3 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-K 2019 (French Ministry of Health)"

This study has been registered on the http://clinicaltrials.gov/ website under *registration number*.

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List of addenda

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17.1 Serious Adverse Events report form

17.2 Include the SCP

SCP must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) or EMEA webite; otherwise, use the SCP from Vidal.

17.3 Questionnaire or scale

CTC-AE -Toxicity Grading scale for determining the severity of adverse event

version **5.0**

Acute GVH according to MAGIC CONSORTIUM 2016

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

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

2. Grade global de GVH aigue (en fonction du stade par organe le plus sévère 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

Chronic GVH according to according to the NIH classification published in 2005 ((selon Filipovitch et al. BBMT 2005)

The diagnosis of chronic GVHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:
A- Classical chronic GvHD in patients with only evidence of chronic GvHD
B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD
C- Late acute GvHD, which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

The severity of chronic GvHD is defined by the number of affected organs.

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		2		1	3		≥2

Manifestation de la 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 génitaux Sécheresse, sténose vaginale, dyspareunie, érythème vulvaire, atrophie 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.

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