Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide in patients with acquired refractory aplastic anemia: a nationwide phase II study
"HAPLO-EMPTY"

INTERVENTIONAL RESEARCH PROTOCOL

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PROTOCOL SIGNATURE PAGE

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

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1 SUMMARY

Full title	Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide in patients with acquired refractory aplastic anemia: a nationwide phase II study
Acronym/reference	HAPLO-EMPTY
Coordinating investigator	Pr Régis Peffault de latour
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Outcomes for patients with severe aplastic anemia (SAA) who are refractory to first-line immunosuppressive therapy (IST) and who lack a matched unrelated donor (MUD) remain poor. Recently, the use of eltrombopag (ELT) has shown blood count improvements in 40% of these patients (1). However, most refractory patients do not respond to ELT or other second-line treatment and are therefore exposed to life-threatening infections, and bleeding. During the past 2 decades, there has been a significant decrease in infection-related mortality in patients with SAA unresponsive to initial IST but clonal evolution including paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML) still occur in the long-term with a grim prognosis. Overall, the overall survival of such patients with acquired refractory SAA to ELT is about 60-70% at 2 years (2). Hematopoietic stem cell transplantation (HSCT) using alternative donor sources (i.e., mismatched unrelated donors, cord blood (CBT), and haplo-identical family donors) may be curative in patients with refractory SAA, despite carrying much higher rates of complications than in transplantations from matched related or unrelated donors. Recently, our group showed that CBT is a valuable curative option for young adults with refractory SAA (3). However, not all patients have available CB and CBT treatment related mortality is high in adult patients. 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). Preliminary results in a little number of patients with refractory SAA at Kings college (London, UK) and John Hopkins (Baltimore, USA) seem promising (4, 5). We retrospectively analyzed data from 36 patients (median age 42 years) transplanted between 2010 and 2017 in Europe on behalf of the SAA working party of the European Blood and Marrow Transplantation group. The 1-year overall survival was about 80% suggesting that this approach might be a valid option in this particular poor clinical situation (6).
Main objective and primary endpoint	**Main objective:** to demonstrate a benefit in term of the 2-year overall survival rate from 60% (historical rates in patients with acquired refractory idiopathic aplastic anemia) up to 80% using haplo-SCT with PTCy. **Primary endpoint:** 2-year overall survival rate of 80%
Secondary objectives and endpoints	**Secondary objectives** Clinical and biological outcomes: - Graft failure, Graft versus Host Disease (GvHD), progression free survival, relapse, non-relapse mortality, Overall Survival - 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 - Incidence of 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 M24 - Incidence of cardiac toxicities at M12 - Overall survival at M12 - Quality of life questionnaire at inclusion, post-transplantation, M3, M6, M12, M24 - Chimerism at M1, M3, M6, M12,M24 - Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation - Ferritin levels at M3, M6, M12, M24
Design of the study	A phase II multicenter, national, prospective cohort study.
Population of study participants	Patients aged from 3 to 35 years with acquired refractory idiopathic aplastic anemia and with an indication of an haploidentical allogeneic hematopoietic stem cell transplantation.
Inclusion criteria	Patients: - Aged from 3 to 35 years old - Suffering from refractory acquired idiopathic aplastic anemia (at least one course of immunosuppression with anti-thymocyte globulin - Absence of geno-identical donor or 10/10 matched donor - With identification of a haploidentical donor (brother, sister, parents, adult children or cousin) - Absence of donor specific antibody detected in the patient with a MFI ≥ 1500 (antibodies directed towards the distinct haplotype between donor and recipient) - With usual criteria for HSCT: ▪ 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 < 150 µmol/L

	- With health insurance coverage - 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) NB : The authorized contraceptive methods are: - For women of childbearing age and in absence of permanent sterilization: oral, intravaginal or transdermal combined hormonal contraception, oral, injectable or transdermal progestogen-only hormonal contraception, intrauterine hormonal-releasing system (IUS), sexual abstinence (need to be evaluated in relation to the duration of clinical trial and the preferred and usual lifestyle of the participants). - For man in absence of permanent sterilization: sexual abstinence, condoms.
Exclusion criteria	Patients: - With morphologic evidence of clonal evolution (patients with isolated bone marrow cytogenetic abnormalities are also eligible **excepted chromosome 7 abnormalities and complex karyotype**). - 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 - Cancer in the last 5 years (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) - Pregnant (βHCG positive) or breast-feeding. - Who received live attenuated vaccine within 2 months before transplantation - Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50% - With heart failure according to NYHA (II or more) - Preexisting acute hemorrhagic cystitis - Renal failure with creatinine clearance <30ml / min - With urinary tract obstruction - Whoreceive the following treatments Phenytoin, Pentostatin, inhibitor of adenoside) - Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up - Under tutorship or curatorship
Transplant modalities	1/**Conditioning regimen** Fludarabine (30mg/m2/day i.v: day -6 to day -2), pre-transplant cyclophosphamide (14.5 mg/kg/day i.v: day -6 and day -5), and Total Body Irradiation (2 Gray on day-1) 2/**Stem cell source** Bone Marrow **3/ GVHD Prophylaxis**

	Rabbit ATG dosed at 0.5 mg/kg on day −9 and 2 mg/kg on days −8 and −7, Cyclophosphamide 50 mg/Kg/day at D+3 and D+4, Tacrolimus (residual 8-12 microg/L) and mycophenolate (MMF) from D+5. In absence of GvHD, MMF will be stopped at D35 and tacrolimus at day 365. 4**/ Prevention of EBV reactivation** Rituximab 150mg/m2 intravenously at Day+5 post HSCT **only** if EBV serology or PCR for EBV of patient and/or donor are positive Each infusion of Rituximab will be preceded by administration of anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine.
Interventions added for the study	No additional test or specific examinations
Expected benefits for the participants and for society	Outcomes for patients with SAA who are refractory to first-line IST and who lack a MUD remain poor. Transplantation is the sole therapeutically valid option. CBT is a valuable curative option for young adults but mortality using this approach is high for adult patients and CB is not always available. Haplo-SCT with PTCy recently showed promising results in this situation and nearly all patients have an available haplo donor (all biologic parents and children of a patient are haplo and each sibling has a 50% chance of being haplo). Moreover, haplo-SCT with PTCy is not only available for almost all patients but also a quick and cheap procedure. This study might thus demonstrate haplo-SCT with PTCy to be a curative option of adult patients with refractory aplastic anemia or children/young patients with no CBT available.
Risks and burdens added by the study	Risks are related to the SCT itself. Cardiac toxicities and hemorrhagic cystitis will be particularly monitored.
Practical implementation	Indication of allograft in context of acquired refractory aplastic anemia
Number of participants included	For an objective of 31 patients to be allo-grafted, we anticipate 35 patients to include.
Number of centres	39 centres in France
Duration of the study	Inclusion period: 36 months Participation period (post-transplant): 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.3 patient/year/centre (0,02 patient/month/centre)
Statistical analysis	**Justification of sample size** We hypothesize the 2-year overall survival (OS) will be of 80% (versus 60% in historical controls). A two-sided, one-sample logrank test calculated from a sample of 31 subjects achieves 80.7% power at a 0.050 significance level to detect a proportion OS of 80% in the new group when the proportion OS in the historic control group is 60% at 2 years. **Terminal analysis** Will be realized after the observation of the required number of events
Funding sources	Ministry of Health - PHRC-N 2019
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Outcomes for patients with SAA who are refractory to first-line IST and who lack a matched unrelated donor (MUD) remain poor. Recently, the use of eltrombopag (ELT) has shown blood count improvements in 40% of these patients (1). However, most refractory patients do not respond to ELT or other second-line treatment and are therefore exposed to life-threatening infections, and bleeding. Moreover, refractory patients have a higher risk of clonal evolution (MDS, LAM) and are also exposed to PNH evolution. Overall, the overall survival of such patients with acquired refractory SAA to ELT is about 60-70% at 2 years (2).
Hematopoietic stem cell transplantation (HSCT) using alternative donor sources (i.e., mismatched unrelated donors, cord blood (CBT), and haplo-identical family donors) may be curative in patients with refractory SAA, despite carrying much higher rates of complications than in transplantations from matched related or unrelated donors (3). Recently, our group showed that CBT is a valuable curative option for young adults with refractory SAA (7). However, not all patients have available CB and CBT treatment related mortality is high in adult patients. 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). Preliminary results in a little number of patients in 3 retrospective studies have shown very encouraging results (4, 5, 6).
Hypothesis: the study presented here aim to demonstrate a benefit in term of the 2-year overall survival rate from 60% (historical rates in patients with acquired refractory idiopathic aplastic anemia) up to 80% using haplo-SCT with PTCy.

2.2 Description of knowledge relating to the condition in question

For idiopathic AA, allogeneic HSCT from a human leukocyte antigen (HLA)–matched related donor (MRD) is the preferred treatment of young patients (3, 2). Long-term outcome has been reported to be excellent (8).
For patients without an HLA identical sibling donor, immunosuppressive therapy (IST) is the preferred option (2). However, 30% to 40% of patients will eventually have relapse or disease will prove to be refractory to IST and those patients will therefore be considered for HSCT using a MUD (3, 9).
In the absence of a MUD, refractory patients will receive eltrombopag (ELT), which has shown blood count improvements in 40% of these patients (1). However, most refractory patients do not respond to ELT or other second-line treatment and are therefore exposed to life-threatening infections, and bleeding. For those patients, HSCT using alternative donor sources (i.e., mismatched unrelated donors, CBT, and haplo-identical family donors) might be discussed.

Alternative HSCT may thus be curative in patients with refractory SAA, despite carrying much higher rates of complications than in transplantations from MRD or MUD (3). Patient age, comorbidities, and alternative HSCT specificities are thus important issues in transplantation decision. Most published series with a meaningful number of patients (reporting >50 alternative HSCTs) are retrospective and involve only pediatric cohorts. The Japanese Marrow Donor Program reported on the role of HLA matching using BM/peripheral blood stem cells in non-malignant disorders in a cohort of 301 patients (median age, 17 years) (10), whereas a similar NMDP/CIBMTR study included 663 patients (median age, 9 years) (11). The EBMT SAAWP unrelated cord blood transplantation study comprised 71 patients (median age, 13 years) (12). Estimated survival in the NMDP/CIBMTR study was 57% at 5 years in 7 of 8 matched HSCT (10). The Japanese study reported better rates of OS; however, possible race- related differences in HLA haplotypes and matching could be important. Three-year OS in a CB retrospective study was 38% (12). Published alternative HSCTs in patients with refractory SAA have thus reported not optimal results in retrospective settings.

Recently, our group showed that CBT is a valuable curative option for young adults with refractory SAA (7). We conducted a prospective nationwide uncontrolled phase II study to assess the efficacy and safety of unrelated cord blood transplantation (CBT) in patients with refractory SAA (APCORD protocol, NCT 01343953). Twenty-six patients (median age: 16 years)

were therefore included. With a median follow-up of 2 years, twenty-three patients were alive at one year, with an overall survival rate of 88.5%, differing significantly from the expected 20% (p<0.0001). However, not all patients have available CB and CBT treatment related mortality is high in adult patients.
Haplo-identical (haplo) related donor Stem Cell Transplantation (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy). Preliminary retrospective results in a little number of patients with refractory SAA at Kings college (London, UK) and John Hopkins (Baltimore, USA) seem promising (4, 5). We retrospectively analyzed data from 36 patients (median age 42 years) transplanted between 2010 and 2017 in Europe on behalf of the SAA working party of the European Blood and Marrow Transplantation group. The 1-year overall survival was about 80% suggesting that this approach might be a valid option in this particular poor clinical situation (6). Those very encouraging 3 retrospective study using haplo-SCT with PTCy in patients with refractory SAA thus support our proposal.

2.3 Summary of relevant pre-clinical experiments and clinical trials

Haplo-SCT with PTCy in patients with refractory SAA prospective clinical trial (Haplo-empty) is justified for the following reason:

1) Outcome of patients with refractory aplastic anemia to IST is generally poor outside transplantation:
In refractory patients, the use of eltrombopag (ELT) alone or within a second course of IST has shown blood count improvements in 40% to 60% of patients (1, 13). However, most refractory patients do not respond to ELT or other second-line treatment and are therefore exposed to life-threatening infections, and bleeding. Moreover, refractory patients have a higher risk of clonal evolution (MDS, LAM) and are also exposed to PNH evolution. Overall, the overall survival of such patients with acquired refractory SAA to ELT is about 60-70% at 2 years (2).
Conclusion 1: most of patients with refractory aplastic anemia are exposed to long-term complications. In the absence of a MUD available and if the patient is eligible to alternative HSCT, haplo-SCT might offer a real chance to cure those patients if they are eligible.
2) Results of haplo-SCT with PTCy retrospective studies in patients with refractory SAA are promising:
Clay and co-authors published the first report on 8 patients with refractory SAA or who have failed a previous HSCT (4). They all received a haplo-SCT with PTCy using a uniform reduced-intensity conditioning regimen. Median age was 32 years (range, 19 to 57). Six of 8 patients engrafted. Graft failure was associated with donor-directed HLA antibodies, despite intensive pre-HSCT desensitization with plasma exchange and rituximab. There was only 1 case of grade II skin graft-versus-host disease. This was the first proof of evidence that haplo-SCT can successfully rescue refractory SAA patients.
The group of Baltimore employed post-transplantation high-dose cyclophosphamide (PTCy) in an effort to safely expand the donor pool in 16 consecutive patients with refractory SAA who did not have a matched sibling donor. Between July 2011 and August 2016, 16 patients underwent allogeneic (allo) BMT for refractory SAA from 13 haploidentical donors. Three patients were transplanted using the same conditioning regimen with PTCy but with unrelated donors (and not haplo identical donor). A non-myeloablative conditioning regimen was used like in the first study but including also antithymocyte globulin. The median age of the patients at the time of transplantation was 30 years (range, 11 to 69). Graft failure, primary or secondary, was not seen in any of the patients. All 16 patients are alive, transfusion independent, and without evidence of clonality with a median follow-up of 21 months (range, 3 to 64). Two patients had grade 1 or 2 skin-only acute GVHD. These same 2 also had mild chronic GVHD of the skin/mouth requiring systemic steroids. One of these GVHD patients was able to come off all IST by 15 months and the other by 17 months. All other patients stopped IST at 1 year. This approach led to 100% engraftment with a low risk of GvHD (5).
The Severe Aplastic Anemia Working Party of the European group for Blood and Marrow Transplantation (EBMT) recently conducted a retrospective analysis of 36 patients (72% male), who received an haplo-PTCy for aplastic anemia in 22 EBMT centers from June 2010 to March 2017. Haplo-PTCy was the first transplantation for 81% patients (second, 11%; third, 8%). All patients received a non-myeloablative preparatory regimen with cyclophosphamide

50mg/kg/day IV on days +3, and +4 post-transplant. The median age was 19.4 years (range 2.5-45.4 years; 58% adults). Cumulative incidence (CI) of neutrophil recovery at day 60 was 78% (64-91) with a median time of 21 days (18-26). Cumulative incidence (CI) of platelet recovery at day 60 was 60% (44-76) with a median time of 31 days (22-185). The CI of grade II-IV acute GvHD was 26% (12-41%) (grade II 19% (7-32%), grade III 6% (0-13%) and no grade IV). CI of chronic GvHD was 17% (5-30) at 1 year (6% (0-13%) extensive) and a CI of 22% (7-37) at 2 years (only limited, there was no new case of extensive cGvHD after one year). With a median follow-up of 24.6 months (15.9 - 38.2), the estimated probability of overall survival (OS) was 78% (64-91) at 1 year and 74% (60-89) at 2 years (6).

Several case reports have shown the interest of such procedure in kids. The publications already presented during the submission process contain some pediatric patients. However, the main publication regarding this category of patients using haplo-identical donors has been published in BBMT in 2020 by the Brazilian group. 87 patients who underwent haplo-PTCy between 2010 and 2019 have been reported. The median patient age was 14 years, most were heavily transfused, and all received previous immunosuppression. All patients received PTCy-based graft-versus-host disease (GVHD) prophylaxis. Most grafts (93%) were bone marrow (BM). The median duration of follow-up was 2 years and 2 months. The median time to neutrophil recovery was 17 days. Primary graft failure occurred in 15% of the patients, and secondary or poor graft function occurred in 5%. The incidences of grade II-IV acute GVHD was 14%, and that of chronic GVHD was 9%. Two-year overall survival and event-free survival (EFS) were 79% and 70%, respectively. This study thus highlights the feasibility and the overall benefit of such approach in kids, again justifying a prospective clinical trial to confirm he results (i.e. Haplo-emtpy).

Conclusion 2: in a population of patients with refractory SAA and no other therapeutic options, retrospective studies suggest haplo-SCT with PTCY as a feasible option with encouraging results.

2.4 Description of the population to be studied and justification for the choice of participants

Young adults with refractory idiopathic aplastic anemia with an available haplo-identical donor (with no or <1500 MFI anti-HLA antibodies) and of course eligible to HSCT will be included.

- Patient age is one of the major factor associated with outcome speaking about alternative HSCT. Older patients are exposed to an unacceptable risk of mortality related to transplantation. Theoretically, 20 years is the acceptable age limit for alternative HSCT in aplastic anemia (3). However, 2 of the 3 retrospective studies published so far reported on patients with a median age of 30 years (6) and 32 years (4). This is the reason why we decided to limit our study to young patients aged less than 35 years.

- High levels of donor-directed anti-HLA allo antibodies most likely explain the non-engraftment in 2 patients of the UK study (4). Intensive desensitization with plasma exchanges and rituximab was insufficient to deplete the antibodies sufficiently to prevent graft rejection. An HLA antibody level of 1500 mean fluorescence intensity was thus suggested to be associated with graft rejection in the setting of T cell depleted haplo-SCT, which will thus be also used for the actual proposal (absence of donor specific antibody (DSA) detected in the patient with a MFI ≥ 1500 -antibodies directed towards the distinct haplotype between donor and recipient).

- Eligibility to HSCT is following usual criteria:
  > 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, ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine clearance >30ml / min

2.5 Identification and description of the transplants modalities

Transplantation modalities are following European guidelines (14), established following excellent results published by deZern et al (5).

a) The conditioning regimen will consisted of Fludarabine (30mg/m2/day i.v.: day -6 to day -2), pre-transplant cyclophosphamide (14.5 mg/kg/day i.v.: day -6 and day -5), and Total Body Irradiation (2 Gray on day -1).
b) The stem cell source will be bone marrow. Granulocyte colony– stimulating factor is given subcutaneously starting on day +5 at 5 mg/ kg/day until the absolute neutrophil count is greater than 1.5 × 109/L for 3 days.
c) GVHD prophylaxis with consisted in rabbit ATG dosed at 0.5 mg/kg on day −9 and 2 mg/kg on days −8 and −7, cyclophosphamide 50 mg/Kg/day at D+3 and D+4. Tacrolimus and mycophenolate (MMF) will begin from D+5. In absence of GvHD, MMF will be stopped at D35 and Tacrolimus at day 365.
d) Moreover, all patients **except patients and their donor with EBV serology and EBV PCR negative** will received 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m2) to prevent Epstein-Barr virus (EBV) reactivation (day+5), as recommended in this situation (15).

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

Outcomes for patients with SAA who are refractory to first-line IST and who lack a MUD remain poor. Transplantation is the sole therapeutically valid option for those patients. CBT is a valuable curative option for young adults but mortality using this approach is high for adult patients and CB is not always available. Haplo-SCT with PTCy recently showed promising results in this situation and nearly all patients have an available haplo donor (all biologic parents and children of a patient are haplo and each sibling has a 50% chance of being haplo). Few retrospective non-controlled studies recently suggest that outcomes after haplo-SCT using PTCy approach might be superior to actual standard of care outside CBT. Moreover, haplo-SCT with PTCy is not only available for almost all patients but also a quick and cheap procedure. This study might thus be a curative option of adult patients with refractory aplastic anemia or children/young patients with no CBT available.

3 OBJECTIVES

3.1 Primary objective

The main objective is to demonstrate a benefit in term of the 2-year overall survival (compared with historical controls)

3.2 Secondary objectives

The secondary objectives will evaluate the following clinical and biological outcomes:
- Graft failure, Graft versus Host Disease (GvHD), progression free survival, relapse, non-relapse mortality, Overall Survival
- Quality of life
- Chimerism
- Immune reconstitution

4 STUDY DESIGN

4.1 *Study endpoints*

Primary endpoint

To demonstrate a benefit in term of the 2-year overall survival rate from 60% (historical rates in patients with acquired refractory idiopathic aplastic anemia) up to 80% using haplo-SCT with PTCy.

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.
- Incidence of 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 M24
- Incidence of cardiac toxicities at M12
- Overall survival at M12
- Quality of life questionnaire (EORTC QLQ-C30- v3 for adult and QQL ped for minor) at inclusion, post-transplantation, M3, M6, M12, M24
- Chimerism at M1, M3, M6, M12, M24
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation
- Ferritin levels at M3, M6, M12, M24

4.2 *Description of research methodology*

Design of the study

A phase II multicenter, national, prospective cohort study.

Number of participating sites

This is a national multi-center study including all adult and pediatric transplant centres of the SFGM-TC 39 centres). Patients will be recruited in the hematology units and referred to the transplant team for the pre-transplant assessment.

Identification of participants

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

5 IMPLEMENTATION OF THE STUDY

5.1 *Screening visit*

The screening visit takes place between D-60 and D-30 before transplant. The investigator checks the eligibility criteria and proposes the study to the patient. Information about the protocol is delivered by the transplant physician in charge of the patient. Concomitantly, the case of the patient will be discussed during the National Multidisciplinary expertise meetings of the French reference centre for aplastic anemia (bi-monthly).

No additional test or specific examinations are performed for research. The patient assessment is performed in the usual care of allogeneic transplant.

A specialized consultation in reproductive medicine should be proposed.

	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)	At the screening visit	At the inclusion visit

5.2 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 original is conserved by the investigator and the third copy for the sponsor.
Patients, after signing written informed consent, will be included by the investigators on eCRF CleanWebTM. The physician will receive a confirmation of the inclusion by email.

- Physical examination

- Reports of patient and disease history
- ECOG assessment
- Sorror score of comorbidities
- Complete physical examination
- 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 test

- 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
- Two pregnancy tests (for women of childbearing age) before starting any treatment*
- Search of anti-HLA antibodies with LUMINEX technology (DSA)
- Chimerism markers' identification
- Marrow aspiration with Karyotype analysis in the 6 weeks before HSCT

** The young girl will be considerate as women of childbearing age following menarche, so pregnancy tests will be performed from the menarche. Serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL(for women of childbearing age) can be used indifferently for young girl.*

· 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

· Imaging :

- Dental radiography
- Total body CT scan

This assessment is performed according to the practice of the investigator.

- Quality of Life (EORTC QLQ-C30- v3) and QQL Ped for minor

- Preservation of the fertility :

1/ Fertility preservation in girls and boys before puberty (Dalle JH et al, 2017).

Before menarche in the girl and before the age of 12-13 years and a Tanner stage P3-T3, it is not possible to consider preserving gametes. Only cryopreservation of gonadal tissue can be considered. These may not be feasible in cases of profound thrombocytopenia or neutropenia due to the high risk of bleeding or infection.

a. For prepubertal girl: cryopreservation of the ovarian cortex, the area containing the oocytes, has been proposed for about 20 years. Pregnancies have been reported after hetero or orthotopic reimplantation of the frozen tissue after allograft for non-malignant pathologybut this is still experimental.

b. For prepubertal boys: it is possible to propose testicular pulp cryopreservation, but as this only contains spermatogonia or spermatozoa from the pubertal period onwards, this is an experimental technique with no practical application to date.

2/ Preservation of fertility in the pubertal subject:

a. For women: it may be proposed a stimulation for the collection of follicles and secondary ovocytes in order to realize either gamete vitrification or in vitro fertilisation followed by embryo preservation (technique reserved for couples). As with cryopreservation of gonadal tissue, the stimulation and transvaginal punctures required for these techniques may be contraindicated by

thrombocytopenia or neutropenia. In a woman with a stable partner, embryo freezing is theoretically possible but rarely compatible with the emergency of management.
b. For men: it is essential to propose a consultation at the CECOS (Centre for the Study and Conservation of Sperm) for the collection and cryopreservation of sperm.

5.3 Follow-up visits post-transplant

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 minimum expected length of hospitalization is 21 days.

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 (2/week) will be performed. Tacrolimus dose adjustment will follow recommendations (see paragraph 7.2)
- Pregnancy tests (for women of childbearing age) at D+5, D+15 and D+45 and if MMF is continued after D+35 (in case of GVHD), a monthly pregnancy test will be performed until the end of MMF treatment
- 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 D+100
- 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 J100. 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.

Patients will be assessed weekly after hospitalization **until D+100 then at M3, M6, M12 and M24** as following:
- Clinical examination, blood cell count, chemistry panel with creatinine and liver test will be performed weekly until D+100, then at each visit (routine follow-up).
- CD3(in case of mixed chimerism ie <95% total population)//CD4/ CD3/ CD8 /B lymphocytes and NK cells protide electrophoreris at J45, J100, J180, M12, M24 and ferritin levels at M1,M3, M6, M12, M24
- Chimerism evaluation at M1, M3, M6, M12,M24
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 : at M12
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC) at D +100
- Chest X-ray weekly until D+100
- **Cardiologic monitoring**: For all patients, a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M12 and M24.
- Safety assessment by collection of all adverse events/serious adverse events at each visit. 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 D100).

- Quality of life at M3, M6, M12, M24

5.4 Expected length of participation and description of the chronology and duration of the study.

Duration of enrolment period	36 months
The length of participation for participants, of which:	
- Duration of follow-up period after graft	24 months
- Total study duration	60 months

The end of the research is defined by the last follow-up of the last allograft patient.

5.5 Table or diagram summarizing the chronology of the study post-transplant

	Screening visit	*Inclusion (baseline visit)*	*D0 = graft*	*Immediate post graft monitoring daily*	*M1*	*M2*	*M3*	*D100*	*M6*	*M12*	*M24*
Information:	*x*										
Signature of the consent form (“non opposition” of the minor patient should be sough depending on the age of the minor)		*x*									
Inclusion exclusion criteria check	*x*	*x*									
βHCG test (before start any treatment)$		*D-17, D-9*	*x*	*D+5, D+15*	*D+45*						
Physical examination (see paragraph 5.2 for complete baseline)		*x*	*x*	*x*	*x*	*x*		*X*	*X*	*x*	*x*
Pre-transplant evaluation		*x*									
Myelogram (Medullar Karyotype)	*X*										
Chest X-ray (weekly until D100)(c) Dental radiography and Total body CT scan (c)		*x*		*x*	*x*	*x*		*X*			
ferritin level					*x*			*X*	*x*	*x*	*x*
Lung function test		*x*						*X*			*x*
Cardiac monitoring (a)		*x*		*x (β)*				*X*		*x*	*x*
Residual rate of Tacrolimus (f)				*X*	*X*	*X*		*X*	*X*		
Blood cell count		*x*	*x*	*x*	*x*	*x*	*X*	*X*	*X*	*x*	*x*
(b) Chemistry panel with creatinine, liver test		*x*	*x*	*X*	*D45*	*x*	*X*	*X*	*X*	*x*	*x*
(d) Aspergillus antigen, PCR for CMV, EBV, adenovirus, HHV-6			*x*	*x*	*x*					*x*	
Chimerism					*x*		*X*		*X*	*x*	*x*
Grading of acute GvHD (e)				*x*	*x*	*x*		*X*			
CD3/CD4/ CD8/ / B lymphocytes (CD19) and NK cells(CD56), and protide electropheris		*x*			*D45*			*X*	*X*	*x*	*x*
Quality of life questionnaire (EORTC QLQ-C30-V3and QQL Ped for minor)		*x*					*X*		*X*	*x*	*x*
Rituximab provided by Sponsor				*D5 post graft if serologyy or PCR of donor or patient are postitive*							
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*

- *$: The pregnancy tests before starting any treatment at D-17, D- 9, then at D+5 (Start MMF), D+15, D+45. If MMF is continued after D+35 (in case of GVHD), a monthly pregnancy test will be performed until the end of MMF treatment.*

(a) monitoring : Electrocardiogram and echocardiography at baseline visit for all the patient ,(β) : 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 D100. 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) Bi-weekly until D+100 (c) : Dental radiography and total body CT scan at baseline : (d)weekly until D100. (e) : weekly during hospitalization and up to D100) ;(f) : Tacrolimus is given for 9 months maintaining trough drug at 10 to 15 µg/L with tapering between 9 and 12 months.

The minimum expected length of hospitalization is 21days .

5.6 Distinction between standard care and study

TABLE: "Standard care" vs. "additional 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**
Treatments	Allogenic transplantation, conditioning regimen, GVHD prophylaxis as well as infection prophylaxis HSCT overall follow-up	Rituximab 150mg/m2 at J5 post-transplant.
Hospitalizations-Consultations		No
Biology test	All biology test included marrow aspiration with Karyotype analysis in the 6 weeks before HSCT	-
Imaging	Dental radiography Total Body CT scan Chest X ray	No

TABLE: volumes authorized to be collected from children

Body weight (kg)	**Circulating total blood volume (ml)**	**Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume**	**Maximum allowable sample volume at single time (ml) - 1% of total blood volume**
5 - 12	480 - 960	14.4 – 28.8	4.8 - 9.6
12 - 20	960 - 1600	28.8 – 48	9.6 -16
20 - 30	1600 - 2400	48 – 72	16 – 24
30 - 70	2400 - 5600	48 – 168	24 – 56

For more information, the research related blood loss as a general rule should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time. In the HaploEmpty research, the biological follow up is identical to the current care in allograft.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria of a recipient

Patients:
- Aged from 3 to 35 years old
- Suffering from refractory acquired idiopathic aplastic anemia (at least one course of immunosuppression with anti-thymocyte globulin)
- Absence of geno-identical donor or 10/10 matched donor

- Absence of donor specific antibody detected in the patient with a MFI ≥ 1500 (antibodies directed towards the distinct haplotype between donor and recipient)
- With identification of a haploidentical donor (brother, sister, parents, adult children or cousin)
- With usual criteria for HSCT:
  - 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 < 150 µmol/L
- With health insurance coverage
- Contraception methods must be prescribed during all the duration of the research and using effective contraceptive methods during treatment and within 12 months for women of childbearing age and 6 months for men of childbearing age after the last dose of cyclophosphamide
- Having signed a written informed consent (2 parents for patients aged less than 18)

The authorized contraceptive methods are:

- For women of childbearing age and in absence of permanent sterilization: oral, intravaginal or transdermal combined hormonal contraception, oral, injectable or transdermal progestogen-only hormonal contraception, intrauterine hormonal-releasing system (IUS), sexual abstinence (need to be evaluated in relation to the duration of clinical trial and the preferred and usual lifestyle of the participants).
- For man in absence of permanent sterilization: sexual abstinence, condoms.

6.2 Exclusion criteria of a recipient

Patients:

- With morphologic evidence of clonal evolution (patients with isolated bone marrow cytogenetic abnormalities are also eligible **excepted chromosome 7 abnormalities and complex karyotype**).
- 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
- Cancer in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix)
- Pregnant (βHCG positive) or breast-feeding.
- Who received live attenuated vaccine within 2 months before transplantation and during the research
- Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50%-
- With heart failure according to NYHA (II or more)
- With urinary tract obstruction
- Preexisting acute hemorrhagic cystitis
- Renal failure with creatinine clearance < 30ml / min
- Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up
- Under tutorship or curatorship
- Who receive the following treatments Phenytoin, Pentostatin, inhibitor of adenoside (see SmPC)*

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

6.3 Clinical selection and Inclusion criteria of a donor

The algorithm for the selection of a haploidentical donor has been defined by the French Society for Stem Cell Transplantation (16, 17, 18).

6.3.1.1 **Inclusion criteria of a donor**

- Intrafamilial donor having 1 HLA haplotype in common with the recipient
- Aged 18 to 70 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 parents of 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. A physician who is not in charge of the recipient will manage the donor before, during, and after the procedure. The follow-up of donors includes routine management and the management of collection-associated adverse events

6.3.1.2 **Exclusion criteria of a donor**

- Presence of donor specific antibody (DSA) with a MFI ≥ 1500 detected in the patient
- Donor who is unable to tolerate a bone marrow harvest or receive general anesthesia, for psychological or medical reasons.
- Donor refusing bone marrow harvest
- Pregnancy in the donor

6.4 Recruitment procedure

The protocol is carried out by the French aplastic anemia of reference centre and the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) (adult and pediatric centres), so most of the members of SFGM-TC will participate to this research. The French biomedicine agency and patients association also support this proposal.

Refractory aplastic anemia concerns about 30% of the 150 new patients per year receiving immunosuppression for this disease in the French Reference / SFGM-TC network, which illustrates the feasibility of the study

	Number of subjects
Total number of subjects to be included	35 (31 allografts)
Number of sites	39
Enrolment period (months)	24
Number of subjects/site	0.8

6.5 Termination rules

Criteria and procedures for prematurely terminating the study procedure

The transplant procedure started cannot be interrupted unless the patient dies.
The investigator must:

- Document the reason(s)

- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraws a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

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

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Death Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved .

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7 TRANSPLANT PROCEDURE

7.1 Transplants modalities

Before to start treatments, two βHCG tests will be done for women of childbearing age. Transplantation modalities are following European guidelines (14), established following excellent results published by deZern et al (5).

7.1.1 Conditioning regimen (5)

The conditioning regimen will consisted of Fludarabine (30mg/m^2/day i.v.: day -6 to day -2), pre-transplant cyclophosphamide (14.5 mg/kg/day i.v.: day -6 and day -5), and Total Body Irradiation (2 Gray on day -1).
However, it is allowed to realize TBI before Fludarabine for local planning reasons.

7.1.2 Type of stem cell source

The stem cell source will be bone marrow. The bone marrow collection is carried out according to the practice of each centre with a target yield of 4×10^8 nucleated cells/kg recipient ideal body weight and infused on day 0, not exceeding the donor volume of 20ml / kg. Granulocyte colony– stimulating factor was given subcutaneously starting on day +5 at 5 µg g/ kg/day until the absolute neutrophil count was greater than 1.5×10^9/L for 3 days.

7.1.3 GVHD prophylaxis

GVHD prophylaxis with consisted in:

a) Rabbit ATG dosed at 0.5 mg/kg on day −9 and 2 mg/kg on days −8 and −7,
b) Cyclophosphamide 50 mg/Kg/day at D+3 and D+4. The injection of cyclophosphamide will be accompanied by systematic injection of Mesna (50 mg / kg) for the prevention of urinary toxicity. The dose of Mesna is twice the one 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 it. Patients must not receive any immunosuppressive agents between the graft infusion and until day +5.
c) Tacrolimus (residual 8-12 microg/L) and mycophenolate mofetil (MMF) will begin from D+5. Tacrolimus is given for 9 months maintaining trough drug at 10 to 15 µg/L with tapering between 9 and 12 months

In absence of GvHD, MMF will be stopped between D35 and D45 . It will be stopped or decreased faster in case of unexpected prolonged cytopenias and in case of digestive disorders (diarrhea). For Tacrolimus, it will be stopped at day 365.

7.1.4 Prevention of EBV reactivation

All patients, **except patients and their donor with EBV serology and EBV PCR negative,** will received 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m2) to prevent Epstein-Barr virus (EBV) reactivation (day+5), as recommended in this situation (15).
Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before administration of Rituximab.

7.1.5 Infection Prophylaxis

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

- Prevention of fungal infections will be done by azols according to ECIL5 (adapted to the SCT risk group)
- Prevention of HHSV and VZV reactivation: aciclovir 250mg/m² x3/day IV then valaciclovir: 500 mg/day po.
- Patients received standard Pneumocystis jiroveci, toxoplasmosis and anti-herpes and varicella prophylaxis for 1 year.
- Prevention of encapsulated bacteria: Oracilline® 50 000 UI/kg x 2/day
- Monthly polyvalent immunoglobulins will be begin in case of hypogammaglobulinemia (<4 g / L)**.**

❖ Management of toxicities:

- Antibiotics (Aminosides, Vancomycine), antivirals (Foscavir), and antifungals (ambisome) will be adapted to the renal function. Voriconazole and le posaconazole will be adapted to the hepatic function,.Cymevan to cytopenias. These adaptations will be regularly carried out in the transplantation department.

7.2 Authorized and prohibited treatments (medicinal, additional medicinal, surgical), *including rescue medications*

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

7.2.1 Authorized treatments

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

7.2.2 Treatments forbidden

Live attenuated vaccines (Yellow fever vaccine, Mumps-Measles-Rubella vaccine) are contraindicated.

7.2.3 Treatments not recommended

- <u>For cyclophosphamide</u>
- Attenuated vaccine (except yellow fever who is forbidden during 6 months after treatment discontinuation.)
- Phenytoin
- Pentostatin
- <u>For Fludarabine</u>
- Pentostatin
- 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 and the other drugs, in reference with the SPC "associations to be considered", will be administered according to the usual practice of the center and at the discretion of the investigator.

7.2.4 Management of relapse

A second transplant is possible depending on the general condition of the patient and the hematological state. The case of the patient must be discussed during the bi-monthly National Multidisciplinary expertise meeting of the French reference center for aplastic anemia.

8 <u>ADDITIONAL MEDICINAL PRODUCTS TO TRANSPLANT PROCEDURE SUPPLIED BY THE SPONSOR</u>

8.1 Rituximab

Posology for clinical trial : Rituximab will be given in one injection) (150 mg/m^2, 330 mg max at Day+5.

Presentation : Rituximab will be provided by the sponsor as 100 mg vials concentrate for solution for infusion. Each box of one vial will be labelled for this study according to the Good Manufacturing Practices under the responsibility of the Département des Essais Cliniques de l'Agence Générale des Equipements et Produits de Santé (AGEPS).

Supplies :
The shipments to the hospital pharmacies will be insured by the DEC of AGEPS.

The hospital pharmacist (with respect to usual procedures) will confirm receipt in writing of all batches of study medication sent and maintain an accurate accounting of them.

Dispensing:
Pharmacies will dispense rituximab infusion bag specifically labelled for each patient on the basis of a specific prescription.

Storage:
Treatments should be stored in the refrigerator (between + 2° C and + 8° C).
Keep the package in the outer carton in order to protect from light.
From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Administration :
The prepared Rituximab solution should be administered as an intravenous infusion through a dedicated line.
Rituximab should be administered under the close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an anti-pyretic and an antihistaminic, should always be given before each administration of Rituximab. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately.

Accountability and destruction: will be made by the CRA at the end of the study in the pharmacies.
A pharmacy manual will describe supplies, storage, dispensing, administration, accountability and destruction.

8.2 Traceability information and monitoring compliance for the Rituximab

Each injection will be recorded on a specific traceability document.

9 EFFICACY ASSESSMENT

9.1 Description of efficacy endpoints assessment parameters

9.1.1 Overall Survival

Overall Survival is defined as the time between HSCT and death.

9.1.2 Progression-free survival

PFS is defined as the time from graft until the occurrence of following events: refractory disease, relapse (cytological) or death from any cause, whatever comes first right

9.1.3 Acute GvHD

Acute GvHD is defined according to MAGIC CONSORTIUM 2016 criteria (19). Each organ is rated with the diagnosis in stage, which allows to 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.

9.1.4 Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 (20). The diagnosis of chronic GVHD is retained 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 organ (Appendix).

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

9.2 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 5.5.

10 SPECIFIC STUDY COMMITTEES

10.1 *Scientific Steering Committee*

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

10.2 *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 Xavier Poiré (Bruxelles , Belgique) end Yves Béguin (Liège, Belgique),
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 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

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

11.1 *Description of Safety endpoints assessment parameters*

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 (19).

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

Adverse events shall be collected according to the schedule in table of paragraph 5.5 of the protocol.

11.3 *Recording and reporting adverse events*

Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalisation or prolongs existing hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

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

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

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, 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 clinical trial or of similar trials.
For studies involving the first administration of a health 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 which have been notified to by the investigator to the sponsor , as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

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

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

Role of the investigator

The investigator must **assess the seriousness 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 thoroughly 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 serious adverse events and thestudy procedure**.**

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· 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 recognised 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

11.3.1.1 **Serious adverse events that require the investigator to notify the sponsor without delay**

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol (section 11.3.1.2.2) and, if applicable, in the investigator's brochure as not requiring notification without any delay. (

A serious adverse event is any untoward medical occurrence that:

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

11.3.1.2 **Specific features of the protocol**

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

- Adverse events deemed "medically significant"(i.e. considered as "serious")

-Non engraftment
-Bacterial, fungal viral and opportunist infectious complications (grade 3-4)
-Veino-occlusive disease (moderate to severe)
-Severe Thrombotic Microangiopathy
-Idiopathic pneumonia (all stages)
-Bronchiolitis obliterans (all stages)
-Severe neurological disorders (coma, convulsion, encepthalitis 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 the investigator becomes aware** of these serious adverse events, in the same manner and within the same deadline as mentioned above.

- ***In utero*** **exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.
The events are reported using a special form, appended to the protocol.

11.3.1.2.2 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 juged 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 .*

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.

11.3.1.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins the procedure of transplant
- throughout the whole follow-up period required for 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).

11.3.1.4 **Procedures and deadlines for notifying the sponsor**

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be de-identified. In addition, the documents must include the following: study acronym, number and participant's initials.

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 participant has left the study.

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 studies which use e-CRF :
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, 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, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

Role of the sponsor

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

11.3.1.5 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** 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, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

- For serious adverse events likely to be related and and considered expected to study procedures:

  - refer to the Investigator's Brochure (separate document) and to the SmPC for cyclophosphamide, fludarabin, mycophenolate mofetil, tacrolimus, 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.

11.3.1.6 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 Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.
Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

11.3.1.7 **Annual safety report**

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

The report must be delivered no later than 60 days after the anniversary of the date of inclusion of first patient.

12 DATA MANAGEMENT

12.1 *Right to access data and source documents*

Data access

In accordance with GCPs:
- 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 or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants 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)

Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [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 their identity 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 *Code Pénal* [French Criminal Code]).

During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.2 Data processing and storage of research documents and data

Data entry

Non-identifying data will be entered electronically via a web browser.

12.3 Data ownership

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

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses

Analysis Populations

The following analysis sets will be considered:

Intent-to-treat: Includes all included subjects. This will refer to the primary analyses

Statistical Methods

As a general strategy, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categoriel characteristics)

Disposition of the Study Subjects

The disposition of subjects will be described the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study was permanently discontinued (including the reasons for discontinuation).

Analysis of Primary Efficacy Endpoint

Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals (CI). Comparaison with the historical controls of 60% at 2 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011. (21)

Analysis of Secondary Endpoints

- Graft failure incidence will be estimated with its 95% CI.
- 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) will be estimated (with its 95% CI) using

Gray's estimator considering death without Neutrophils and platelets engraftment respectively as competing risks.

- Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions will be described using median and interquartile range
- The incidence of use of growth factors for poor hematopoietic reconstitution will be estimated with its 95% CI
- 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) will be estimated (with its 95% CI) using Gray's estimator considering death without acute GvHD as competing risks.
- Chronic GvHD incidence (date and grading at M24) will be estimated (with its 95% CI) using Gray's estimator considering death without chronic GvHD as competing risks
- Relapse incidence at M12 and M24 using Gray's estimator considering death without relapse as competing risks.
- Progression free survival at M12 and M24 will be estimated using the Kaplan-Maier's estimator with its 95% CI
- Incidence of CMV and EBV infection at M12 will be estimated using the Kaplan-Maier's estimator with its 95% CI.
- Severe infections incidence (CTAE grade 3-4) à M3, M6, M12 and M24 will be estimated with its 95% CI.
- Non-relapse mortality M24 will be estimated (with its 95% CI) using Gray's estimator considering relapse as competing risks.
- Incidence of cardiac toxicities at M12 will be estimated with its 95% CI
- Quality of life questionnaire (EORTC QLQ-C30- v3) at inclusion, post-transplantation, M3,M6, M12, M24 will be described using median and interquartile range
- Chimerism at M1, M3, M6, M12, M24 will be estimated with its 95% CI
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation will be described using median and interquartile range
- Ferritin levels at M3, M6, M12, M24 will be described using median and interquartile range.

13.2 Calculation hypotheses for the number of participants required and the result

We hypothesize the 2-year overall survival (OS) will be of 80% (versus 60% in historical controls). A two-sided, one-sample logrank test calculated from a sample of 31 subjects achieves 80.7% power at a 0.050 significance level to detect a proportion OS of 80% in the new group when the proportion OS in the historic control group is 60% at 2 years (22).

Anticipated level of statistical significance
All tests will be two-sided with a type I error rate fixed at 0.05.

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

All the effort will be done to avoid missing data in the outcomes.
Confirmatory analyses will be performed by using multiple imputation by chained equation or using joint Bayesian modelling to impute outcome as well as missing characteristics.

13.4 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 database. All modifications of the initial plan will be submitted to the scientific

committee, the investigator and the sponsoras well as regulatories. All modifications to the original protocol will be described in the SAP.

14 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

14.1 *General organisation*

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

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

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

Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate 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 centre 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.

14.2 Quality control

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

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

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

- management of the treatments used

14.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and 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 a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, 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, the data are immediately verified as they are entered, thanks to consistency checks. To this end, 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 issued to the sponsor.

14.4 Management of non-compliances

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

These non-compliances will be managed in accordance with the sponsor's procedures.

14.5 Audits/inspections

The investigators agree to consent to 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 grounds of medical secrecy.

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

The persons who manage and monitor the study agree to comply with the sponsor's 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, including the storage of the data used or produced as part of the study.

14.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

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

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI 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.

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15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

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.

15.2 Prohibition from participating in another clinical study or exclusion period set after the study.

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. Indeed, participation in another interventional trial can be considered by investigator as long as it does not influence the main criteria of this present research.

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.

15.3 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

15.4 Legal obligations

Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance

with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

Procedures relating to data protection regulations

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

Choose one of the two options proposed (A or B), with the pre-drafted text and delete the option not retained. Only to be completed relative to reasons for exclusion from the MR (Reference Methodology).

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

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

Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 30 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - the ANSM authorisations and CPP (Research Ethics Committee) decisions
    - any correspondence
    - the enrolment list or register
    - the appendices specific to the research
    - final study report
- The data collection documents

16 FUNDING AND INSURANCE

16.1 *Funding sources*

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

16.2 *Insurance*

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled 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).

17 PUBLICATION RULES

The author(s) of any publication relating to this study must include the APHP among their affiliations and name the sponsor AH-HP (DRCD) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor.

17.1 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 unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address 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

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

“The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l’Innovation)”

17.3 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 2019 (French Ministry of Health)”*

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

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Leonardo Javier Arcuri, Samir Kanaan Nabhan, Renato Cunha, Samantha Nichele, Andreza Alice Feitosa Ribeiro, Juliana Folloni Fernandes, Liane Esteves Daudt, Ana Luiza Melo Rodrigues, Celso Arrais-Rodrigues, Adriana Seber, Elias Hallack Atta, Jose Salvador Rodrigues de Oliveira, Vaneuza Araujo Moreira Funke, Gisele Loth, Luiz Guilherme Darrigo Junior, Alessandra Paz, Rodolfo Froes Calixto, Alessandra Araujo Gomes, Carlos Eduardo Sa Araujo, Vergilio Colturato, Belinda Pinto Simoes, Nelson Hamerschlak, Mary Evelyn Flowers, Ricardo Pasquini, Vanderson Rocha, Carmem Bonfim.Biol Blood Marrow Transplant 26 (2020) 23112317,

24-Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide

Amy E. DeZern,1,2 Marianna L. Zahurak,1,3 Heather J. Symons,1,4 Kenneth R. Cooke,1,4 Gary L. Rosner,3 Douglas E. Gladstone,1
Carol Ann Huff,1 Lode J. Swinnen,1 Philip Imus,1 Ivan Borrello,1 Nina Wagner-Johnston,1 Richard F. Ambinder,1 Leo Luznik,1
Javier Bolaños-Meade,1 Ephraim J. Fuchs,1 Richard J. Jones,1,2 and Robert A. Brodsky1,2
1Department of Oncology, Sidney Kimmel Cancer Center, Baltimore, MD; 2Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD; and
3Department of Oncology Biostatistics and 4Division of Pediatric Oncology, Sidney Kimmel Cancer Center, Baltimore, MD

25-State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) inBaden, Austria, 29–30 September 2015

J-H Dalle1,28, G Lucchini2,28, A Balduzzi3,28, M Ifversen4,28, K Jahnukainen5,6,28, KT Macklon7,28, A Ahler8,28, A Jarisch9,28, M Ansari10,11,28, E Beohou12,28, D Bresters13,28, S Corbacioglu14,28, A Dalissier12,28, C Diaz de Heredia Rubio15,28, T Diesch16,28, B Gibson17,28, T Klingebiel9,28, A Lankester13,28, A Lawitschka18,28, R Moffat8,28, C Peters18,28, C Poirot19,28, N Saenger20,28, P Sedlacek21,28, E Trigoso22,28, K Vettenranta23,28, J Wachowiak24,28, A Willasch9,28, M von Wolff25,28, I Yaniv26,28, A Yesilipek27,28 and P Bader9,28 on behalf of the
EBMT Paediatric Diseases Working Party

26- Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia

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1Department of Oncology, Sidney Kimmel Cancer Center, Baltimore, Maryland 2Department of Medicine, Division of Hematology, Johns Hopkins University, Baltimore, Maryland 3Department of Oncology Biostatistics, Sidney Kimmel Cancer Center, Baltimore, Maryland 4Division of Pediatric Oncology, Sidney Kimmel Cancer Center, Baltimore, Maryland.

19 LIST OF ADDENDA

19.1 List of investigators (separate documents)

19.2 Serious Adverse Events notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur une Préparation de Thérapie Cellulaire/Tissu/Organe**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0287

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (4 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons

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

1. Identification de la recherche	
Acronyme : **HAPLO-EMPTY**	**Date de notification :** |__|__| |__|__| |2|0|__|__| (jj mm aaaa)
Code de la Recherche : APHP 200004	**Date de prise de connaissance de l'EIG par l'investigateur :** |__|__| |__|__| |2|0|__|__| (jj mm aaaa)
Risque : D	

Titre complet de la recherche :

Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide in patients with acquired refractory aplastic anemia: a nationwide phase II study

2. Identification du centre investigateur	
Nom de l'établissement : ..... Ville et code postal : ..... Service :	Investigateur (nom/prénom) : ..... Tél : .....

3. Identification et antécédents de la personne se prêtant à la recherche	
Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)	**Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :**
Sexe : ☐ M ☐ F Poids : |__|__|__| kg Taille : |__|__|__| cm	Date de naissance : |__|__| |__|__| |__|__|__|__| (jj mm aaaa) Age : |__|__|__|ans
Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)	

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-

Date de la greffe : |__|__| |__|__| |__|__|__|__| Ou non réalisée : ☐ Conditionnement de la greffe : Conforme au protocole oui ☐ non ☐ Si non : indiquer la modification : …… Nombre de cellules administrées : x 10^8 TNC/kg receveur	**Prophylaxie de la GVHD** : conforme au protocole: oui ☐ non ☐ Si applicable préciser la date d'arrêt : mycophenolate mofetil arrêté le |__|__| |__|__| |__|__|__|__| ☐NA tacrolimus arrêté le |__|__| |__|__| |__|__|__|__| ☐NA Si non conforme au protocole : indiquer la modification (notamment, doses, dates d'administration, raison) …… …… …… ……

4. Prévention EBV avant la survenue de l'EIG

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie	Posologie	Date d'administration *(jj/mm/aaaa)*
Rituximab	IV	…… mg/m2	: |__|__| |__|__| |_2_|_0_|__|__|

Acronyme : **HAPLO-EMPTY**

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

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

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

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

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

6. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire …… …… ……	**Organe(s) concerné(s) :** …… …… …… …… …… ……
Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__| Préciser lesquels : …… ……	

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Degré de sévérité
En cas de **GvHD chronique** (selon NIH classification 2005):
☐ Léger ☐ Modéré ☐ Sévère
En cas de **GvH aigue** (selon *MAGIC CONSORTIUM 2016):*
0 : ☐ 1 : ☐ 2 : ☐ 3 : ☐ 4 : ☐

Autres cas : CTC-AE (v5.0) : ☐1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Critères de gravité :
☐ Nécessite ou prolonge l'hospitalisation :
du |__|__| |__|__| |_2_|_0_|__|__|
au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

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

Des mesures symptomatiques ont-elles été prises ?

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

.....

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

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

Si oui, joindre le certificat de libération du lot concerné et le formulaire de biovigilance si disponible.

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

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

L'évènement fait-il suite à :

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

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

Evolution de l'événement

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

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

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

☐ **Evolution inconnue**

7. Autre(s) étiologie(s) envisagée(s)

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

8. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....

…… ……

9. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)
Lié à la recherche : ☐ **Oui :** ☐ **au conditionnement de la greffe (préciser le(s) médicament(s)) :** …… ☐ **à la greffe de CSH** ☐ **au rituximab** ☐ **à la prophylaxie de la GVHD (préciser le(s) médicament(s)) :** …… ☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche** ☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** …… ☐ **à une maladie intercurrente, laquelle :** …… ☐ **autre, préciser :** ……

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

19.3 Pregnancy notification form

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

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

1. Identification de la recherche
Acronyme : **HAPLO-EMPTY** **Code de la Recherche : APHP 200004**

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

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

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

Titre complet de la recherche :
Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide in patients with acquired refractory aplastic anemia: a nationwide phase II study

2. Identification du centre investigateur	
Nom de l'établissement : …… Ville et code postal : …… Service : ……	Investigateur (nom/prénom) : …… Tél :
3. Identification de la personne présentant une grossesse	
	Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom
Date de naissance : |__|__| |__|__| |__|__|__|__|
Date de signature du consentement : __|__| |__|__| |_2_|_0_|__|__|

Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom
Date de naissance : |__|__| |__|__| |__|__|__|__|
Date de signature du consentement :
|__|__| |__|__| |_2_|_0_|__|__|

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser 53uncti OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :

Chirurgicaux :

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

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

5. Procédures de la recherche pendant la grossesse ou s'il s'agit une exposition paternelle

Date de la greffe : |__|__| |__|__| |__|__|__|__| Ou non réalisée : ☐

Conditionnement de la greffe : conforme au protocole oui ☐

☐ non, indiquer la modification : ……
……

Source de cellules : Moelle Osseuse : oui ☐ non ☐

Nombre de cellules administrées : Conforme : oui ☐ non ☐, si non précise
……

Prophylaxie de la GVHD : conforme au protocole : oui ☐ non ☐
Si non : indiquer la modification (notamment, doses, dates d'administration, raison) ……
……
……

	Date d'administration ou non administré	Voie	Posologie
Rituximab	|__|__| |__|__| |_2_|_0_|__|__| ou ☐ Non administré	**IV**	…… mg/m2

Acronyme :

EMPTY

HAPLO-

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-

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

8. Médicament(s) concomitants administré(s) dans le cadre du soin

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

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

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

9. Suivi de la grossesse

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

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

10. Grossesse en cours ☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)

ou issue de la grossesse ☐ (compléter ci-dessous)

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

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

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

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

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

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

11. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

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

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

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

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

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

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

19.4 Questionnaires or scale

19.4.1 Quality of life questionnaires

EORTC QLQ-C30-V3 for adult and QLQ Ped for minor **(***separate documents*)

19.4.2 Scale

19.4.2.1 CTC-AE -Toxicity Grading scale for determining the severity of adverse event
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

19.4.2.2 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

19.4.2.3 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