Up-front Matched Unrelated Donor Transplantation in Pediatric Patients with Idiopathic Aplastic Anemia: a phase II feasibility study
"UPFRONT-MUD"

INTERVENTIONAL RESEARCH PROTOCOL

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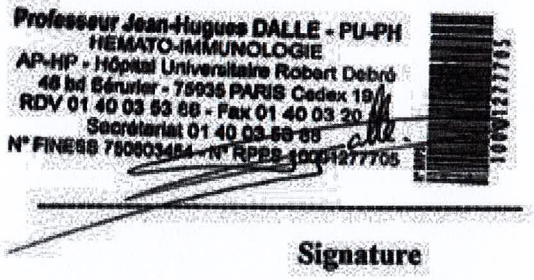
12/ JUL/ 2022

Date
(dd/MMM/yyyy)



Signature

I confirm that I have read this protocol and its attachments, and that I agree to conduct the study in compliance with the protocol, applicable laws and regulations.

I agree to ensure that all associates, colleagues and employees, as well as local physicians and HCP assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that they receive the appropriate information throughout the study

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1 SUMMARY

Full title	Up-front Matched Unrelated Donor Transplantation in Pediatric Patients with Idiopathic Aplastic Anemia: a phase II feasibility study
Acronym/reference	**UPFRONT-MUD**
Coordinating investigators	Pr Jean-Hugues Dalle, Pr Régis Peffault de Latour
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Pediatric patients with idiopathic aplastic anemia (AA) respond better than adults to immunosuppressive therapy (IST) but the long-term risks of relapse, ciclosporine dependence, and clonal evolution are high. UK investigators reported a 5-year estimated failure-free survival (FFS) after IST of 13.3%. In contrast, in 44 successive children who received a matched unrelated donor (MUD), hematopoietic stem cell transplantation (HSCT), there was an excellent estimated 5-year FFS of 95%. Forty of these children had previously failed IST. Because of those excellent results, up-front fully matched unrelated donor (MUD) hematopoietic stem cell transplantation (HSCT) became an attractive first-line option. In 2005 to 2014, a UK cohort of 29 children with idiopathic AA thus received MUD HSCTs as first-line therapy (they did not receive IST prior to HSCT). Results were excellent, with low Graft versus Host Disease rates and only 1 death (idiopathic pneumonia). This cohort was then compared with historical matched controls, transplanted or not. Outcomes for the up-front unrelated cohort HSCT were similar to Matched Related Donor HSCT and superior to IST and unrelated HSCT post-IST failure. Since then, many investigators are offering up-front MUD HSCT in pediatric patients worldwide. However, those results should be treated with extreme caution: 1) the design is retrospective; 2) the excellent up-front MUD HSCT may arise from the use of alemtuzumab in the conditioning regimen (alemtuzumab is not easily available worldwide) and 3) there was no formal quality-of-life assessment. Moreover, this strategy is highly dependent on donor identification (Caucasian patients have the highest likelihood of having a MUD) and donor availability. We thus don't know how many patients did not eventually receive HSCT because of the risk of infections/complications caused by unexpected donor delays or cancellation. Prospective trials are thus urgently needed to address the feasibility of such procedure, in term of timing (delay to offer MUD HSCT) and conditioning regimen (nothing is known of the use of other regimens, non alemtuzumab-based, in this setting).
Main objective and primary endpoint	**Main objective:** To realize up-front HSCT within 2 months once a MUD has been identified

	Primary endpoint: Upfront MUD HSCT effectively performed within 2 months (60 days) after identification of a MUD
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 (first day of 3 consecutive days with neutrophils >0.5 G/L and first day of 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. - 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 - Overall survival at M24 - Quality of life questionnaire (PedQQL) at inclusion, post-transplantation, M3, M6, M12, M24 - Chimerism at M1, M3, M6, M12, - 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	Phase II multicenter, national, prospective cohort study
Population of study participants	Pediatric patients aged less than 18 years with idiopathic aplastic anemia and an indication for treatment (severe aplastic anemia or moderate aplastic anemia requiring transfusions).
Inclusion criteria	**Patients**: - age<18years old - Pediatric patients aged less than 18 years with idiopathi aplastic anemia and an indication for treatment (severe aplastic anemia or moderate aplastic anemia requiring transfusions) - With a good probability to have a HLA-10/10 matched unrelated donor available (the patient needs to have at

	least 3 MUD identified within the book BMDW (Bone Marrow Donors Worldwide) or using the easy match software to be included) - With usual criteria for allo-SCT: > Lansky >70% for those below 16 years and Karnofsky > 70% for those above 16 years > No severe and uncontrolled infection > Adequate organ function: ASAT and ALAT ≤ 5N*, total bilirubin ≤ 2N, creatinine clearance > 70% of higher normal values for age. - With health insurance coverage (bénéficiaire ou ayant droit). - Contraception methods** for young girl and men of childbearing age must be prescribed during all the duration of the research. - Parents having read and understand the information note and signed a written informed consent (the patient's agreement depending on his age will be sought) *because typical presentation of aplastic anemia post-hepatitis ** 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). - For man in absence of permanent sterilization: condoms
Exclusion criteria	**Patients:** - With a matched related donor available - 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 - Renal failure with creatinine clearance below 70% of higher normal values for age - Pregnant (βHCG positive) or breast-feeding - With Heart failure according to NYHA (II or more) - Preexisting acute hemorrhagic cystitis - Urinary tract obstruction - Yellow fever vaccine within 2 months before transplantation - Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up (depending of his age and understanding). - With Contraindication to treatments used during the research
Transplant Modalities	1/ **<u>Conditioning regimen</u>** • For patients aged less than 14 years Fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3), and

	Anti-thymocyte globulin (3.75 mg/Kg/day: day -6 to day -3). • For patients aged 14 or more Fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3), Anti-thymocyte globulin (3.75 mg/Kg/day: day -4 and day -3) and Total Body irradiation 2 gray (day -1). However, it is allowed to realize TBI before Fludarabine for local planning reasons: TBI day -5, anti-thymocyte globulin D-4 et D-3, Fludarabine D-4 to D-1. TBI D-5, , Fludarabine D-4 to D-1 Cyclophosphamide D-4 to D-1. 2/ **Stem cell source** Only Bone Marrow With a minimal target dose of $4x10^8$ nucleated cells/kg recipient ideal body weight. If the graft is less rich than the minimum target dose, it can be administered at the discretion to the physician. 3/ **GVHD Prophylaxis** GVHD prophylaxis with consist in the association of cyclosporine plus methotrexate (MTX): IV Cyclosporine 3 mg/kg/j at Day -1 until 1 year post HSCT plus Methotrexate (MTX) IV 10mg/m2 given on day+1, and subsequently at 8 mg/m2 on days +3 and day+6. **Prevention of EBV reactivation** Rituximab 150mg/m2 IV at Day+5 post HSCT. 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 examination
Expected benefits for the participants and for society	Long-term outcome after IST in pediatric patients with idiopathic AA is poor. Transplantation approach allows curing definitively patients who can then come back to normal life. However, HSCT is usually associated with an unpredicted risk of morbidity and mortality, especially using unrelated donor. The standard conservative approach is to initiate a donor search in all pediatric patients and to pursue MUD HSCT upon donor availability should IST be ineffective, usually at 3 to 6 months post IST. The study presented here will address the feasibility of up-front MUD HSCT in pediatric patients with idiopathic AA, in term of timing (delay to offer MUD HSCT) and conditioning regimen (nothing is known of the use of other regimens, non alemtuzumab-based, in this setting). In case of success, up-front MUD HSCT will be safely used to cure pediatric patients with aplastic anemia, avoiding long-term complications of IST.
Risks and burdens added by the study	The major risk is donor cancellation and thus prolonging the period of aplasia, being at risk of infections or

	hemorrhage. This is why we decided to include an interim analysis.
Practical implementation	Indication of up-front MUD HSCT in context of idiopathic aplastic anemia in pediatric patients
Number of participants included	25 patients with an interim analysis after 12 inclusions
Number of centres	13 centres in France
Duration of the study	Inclusion period: 36 months Participation period (post-HSCT): 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.6 patient/year/centre (0,05 patient/month/centre)
Statistical analysis	**Justification of sample size** We use the Simon Minimax Two-Stage Phase 2 design, to demonstrate success (primary outcome) in 70% of patients (to consider treatment as a valuable option) against less than 45% (considered as unacceptable). **Interim analysis** An interim analysis will be performed after 12 inclusions: the trial will be terminated if 5 or fewer do not receive Upfront MUD HSCT, then the study ends with conclusion of inefficacy. Otherwise, inclusions are pursued until a total of 25 patients. To conclude treatment efficacy, at least 16 successes should be identified among the 25 patients.
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

Long-term outcome after IST patients with idiopathic AA is not optimal (1). Excellent results of up-front MUD HSCT have been recently reported in a cohort of 29 children with idiopathic AA using a campath (alemtuzumab)-based regimen (2). However, those results have some limitations: retrospective design, use of alemtuzumab (not easily available worldwide), and no formal quality-of-life assessment. In addition, a security alert regarding alemtuzumab was published by ANSM during spring 2019. Moreover, this strategy is highly dependent on donor identification and donor availability. In the absence of a prospective trial, those results are thus highly discussable. The standard more conservative approach is to initiate a donor search in all pediatric patients and to pursue MUD HSCT upon donor availability should IST be ineffective, usually at 3 to 6 months post IST.
Hypothesis: the study presented here will address the feasibility of up-front MUD HSCT in pediatric patients with idiopathic AA, in term of timing (delay to offer MUD HSCT) and number of patients eventually transplanted using this strategy. The success will be defined by an upfront MUD HSCT effectively performed within 2 months (60 days) after identification of a MUD in 70% or more of the eligible patients.

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, 4). Long-term outcome has been reported to be excellent with roughly 90% of overall survival at 5 years (5). For patients without an HLA identical sibling donor, immunosuppressive therapy (IST) is preferred (4). However, 30% to 40% of patients will eventually relapse or disease will be primarily refractory to IST and those patients will therefore be considered for HSCT using a MUD. However, being transplanted after several months of IST is associated to high-risk of both infectious complications and organ damages like ciclosporin related renal injury. Other alternative stem cell sources, including HLA-mismatched UD (MMUD), unrelated cord blood (CB), or haploidentical (haplo) familial donors are considered experimental so far (alternative HSCTs).

MUD HSCT improved to such an extent that OS of MUD HSCT for idiopathic SAA is not statistically inferior to sibling transplantations (6). This improvement has been largely attributed to better donor selection through allele matching, progress in supportive care and GVHD prophylaxis, incorporation of fludarabine in conditioning regimens, and the addition of low-dose TBI (3). Patients undergoing MUD grafts, however, remain at greater risk of acute and chronic GVHD (twice that of MRD HSCT), which may significantly alter their quality of life, reason why in the absence of an HLA identical sibling donor, first-line IST is recommended and transplantation from a MUD is considered after failure to respond to 1 course of IST, better within the first year between diagnosis and HSCT (7).

2.3 Summary of relevant pre-clinical experiments and clinical trials

Up-front MUD HSCT in pediatric patients should be addressed through a prospective clinical trial for the following reason:
1) Outcome after IST is associated with possible long-term complications (1):
The Severe Aplastic Anemia Working Party of the European group of Blood and Marrow Transplantation (SAAWP EBMT) led a prospective randomized study on treatment of 192 SAA patients with ATG and Cyclosporine (CSA) with and without G-CSF, which showed that G-CSF added to ATG/CSA has no significant impact on overall survival (OS), event free survival (EFS), relapse, or death rates (8). However, a follow-up of that study, 16 years after initiation,

has recently been published (1). Patients were carefully updated for the following events: refractory status, relapse, long-term events such as clonal evolution to paroxismal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), solid Cancer occurrence, osteonecosis or kidney failure and death. Overall, less than 25% of patients were alive and event-free 15 years after initial treatment. Similar report has been published in 43 consecutive children with idiopathic SAA who all received rabbit ATG as first line IST with a 5-year estimated failure-free survival (FFS) of 13.3% (95% CI 4·0 to 27·8).
Conclusion 1: most of pediatric patients with idiopathic aplastic anemia treated with IST in the absence of a HLA MRD are not cured and exposed to long-term complications.

2) Results of MUD have improved drastically in recent years, especially in kids (9):
As stated previously, OS of MUD HSCT for idiopathic SAA is not statistically inferior to sibling transplants (see section 2.2). However, patients remain exposed to a greater risk of acute and chronic GVHD (twice that of MRD HSCT). This risk is lower in pediatric patients when compared with adult patients (10, 11). Using the French Society of Bone Marrow Transplantation and Cell Therapies registry, we analyzed all consecutive patients (n=139) who underwent a first allogeneic transplantation for refractory idiopathic severe aplastic anemia from an unrelated donor between 2000 and 2012. In an adjusted multivariate model, age over 30 years (Hazard Ratio=2.39; P=0.011), time from diagnosis to transplantation over 12 months (Hazard Ratio=2.18; P=0.027) and the use of a 9/10 mismatched unrelated donor (Hazard Ratio=2.14; P=0.036) were independently associated with worse overall survival. Accordingly, we built a predictive score using these three parameters, considering patients at low (zero or one risk factor, n=94) or high (two or three risk factors, n=45) risk. High-risk patients had significantly shorter survival (Hazard Ratio=3.04; P<0.001). The score was then confirmed on an independent cohort from the European Group for Blood and Marrow Transplantation database of 296 patients, with shorter survival in patients with at least 2 risk factors (Hazard Ratio=2.13; P=0.005). This study confirmed that patients with SAA, refractory to IST, should be transplanted in the first year after diagnosis if a MUD is identified (7). Moreover, results of MUD HSCT in pediatric patients with refractory aplastic anemia are outstanding. In 44 successive children who received a 10 out of 10 antigen (HLA-A, -B, -C, -DRB1, -DQB1) MUD HSCT there was an excellent estimated 5-year FFS of 95% (95% CI 81·38–98·74). Forty of these children had failed IST previously. HSCT conditioning was a fludarabine, cyclophosphamide and alemtuzumab (FCC) regimen. There were no cases of graft failure. Median donor chimerism was 100% (range 88–100%) (9).
Conclusion 2: MUD HSCT following IST failure offers an excellent outcome, especially in kids. The last study from UK investigators (9) suggested for the first time that if a suitable MUD can be found quickly, MUD HSCT may be a reasonable alternative to IST in pediatric patients.

3) First clinical evidences of up-front MUD HSCT in pediatric patients with SAA are very encouraging:
Twenty-nine pediatric patients with SAA received up-frond unrelated donor transplantation (24 MUD and 5 MMUD) in United Kingdom. Outcomes were excellent with only two events, consisting of one primary graft failure following a HLA-A MMUD HSCT (with pre-existing anti donor HLA-A antibodies) and one death following MUD HSCT, due to idiopathic pneumonia syndrome after engraftment. The other 27 patients were in complete remission at last follow-up. The 2-year OS for the whole cohort was 96.4% and the 2-year EFS was 92.5%. The median whole blood donor chimerism at last follow-up was 100% (range 88–100%; n = 29) and the median donor T-cell chimerism was 96.5% (range 91–100%; n = 8). This cohort was then compared to matched historical controls who had undergone first-line therapy with a matched sibling/family donor (MSD) HSCT (n = 87) or IST with horse antithymocyte globulin and cyclosporin (n = 58) or second-line therapy with unrelated donor HSCT post-failed IST (n = 24). The 2-year event-free survival in the upfront cohort was 92.5% compared to 87.4% in MSD controls (P = 0.37), 40.7% in IST controls (P = 0.0001) and 74.9% in the unrelated donor HSCT post-IST failure controls (n = 24) (P = 0.02) (2).

Conclusion 3: Outcomes for upfront-unrelated donor HSCT in pediatric idiopathic SAA were similar to MSD HSCT and superior to first line IST and unrelated donor HSCT post-IST failure, suggesting again front-line therapy with MUD donor HSCT might be a novel treatment approach in pediatric patients who lack a HLA MRD.

4) Why a clinical trial is mandatory to address this question?
Results of up-front MUD in pediatric patients with SAA should clearly be treated with caution. The design is retrospective, the excellent up-front UD HSCT may arise from the use of the FCC regimen (alemtuzumab is not easily available worldwide), and there was no formal quality-of-life assessment. Moreover, this strategy is highly dependent on donor identification (Caucasian patients have the highest likelihood of having a MUD) and donor availability, with the risk of infections/complications caused by unexpected donor delays. We thus need to know how many patients were supposed to receive an up-front MUD but never received it because of unexpected complications before HSCT (infections or hemorrhage) or donor cancellation, reason why a prospective trial is mandatory. Moreover, alemtuzumab is not easily accessible in France and nothing is known prospectively of the use of other regimens at least first line in this setting.
Conclusion 4: The study presented here will address the feasibility of up-front MUD HSCT in pediatric patients with idiopathic AA, in term of timing (delay to offer MUD HSCT) and conditioning regimen (use of other regimens, non alemtuzumab-based, in this setting).

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

Pediatric patients with idiopathic aplastic anemia with a good probability to have an HLA-10/10 matched donor available (in the absence of a HLA-MRD available) and of course eligible to HSCT will be included.

- Pediatric patients are more exposed to long-term complications following IST because of a longer life expectancy than their adult counterpart. As stated before (see section 2.3.2), this population is also exposed to a lower risk of morbidity and mortality following MUD HSCT. Results on up-front MUD have already been published in a few number of patients (see section 2.3.3).
- The patient needs to have at least 3 MUD identified outside the book or using the easy match software to be included to avoid as much as possible last minute donor cancellation. We thus don't want to expose patients included in the trial to a longer period of aplasia and thus to a higher risk of infections or hemorrhage. This is also why we will run an interim analysis after 12 patients included to verify the absence of an unacceptable rate of HSCT cancellation.
- Eligibility to HSCT is following usual criteria:
  > Lansky >70% for those below 16 years and Karnofsky > 70% for those above 16 years
  > No severe and uncontrolled infection
  > Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, ASAT and ALAT ≤ 5N, total bilirubin ≤ 2N, creatinine clearance > 70% of higher normal values for age.

2.5 Identification and description of the investigational medication or medications

Transplantation modalities are following European guidelines (12, 13). In the absence of an easy access to alemtuzumab, which is possible only in UK, European experts recommend the following transplantation procedure:

a) The conditioning regimen will consisted for patients aged less than 14 years of Fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3), and rabbit Anti-thymocyte globulin (3.75 mg/Kg/day: day -6 to day -3). For patients aged 14 or more, the conditioning regimen will consisted of fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3),

rabbit Anti-thymocyte globulin (3.75 mg/Kg/day: day -4 and day -3) and Total Body irradiation 2 grays (day -1).

b) The stem cell source will be only bone marrow
c) GVHD prophylaxis with consisted in the association of cyclosporine plus methotrexate (MTX)
d) All patients will receive 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m2) to prevent Epstein-Barr virus (EBV) reactivation (day+5) (14).

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

Long-term outcome after IST in pediatric patients with idiopathic AA is poor. Transplantation approach allows curing definitively patients who can then come back to normal life. However, HSCT is usually associated with an unpredicted risk of morbidity and mortality, especially using unrelated donor. Excellent results of up-front MUD HSCT have been reported by UK investigators but in few patients, with a retrospective study design, using an alemtuzumab-based regimen (which is not easy to have outside UK).

The major benefit for patients is to avoid long-term complications after IST by offering them a real curative option. In case of success, up-front MUD HSCT will be safely use for the treatment of pediatric patients with aplastic anemia.

The major risk is donor cancellation and thus prolonging the period of aplasia, being at risk of infections or hemorrhage. This is why we decided to include an interim analysis.

3 OBJECTIVES

3.1 Primary objective

The main objective is to offer up-front HSCT within 2 months once a MUD has been identified in pediatric patients with aplastic anemia.

3.2 Secondary objectives

The secondary objectives are to 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

MUD Transplantation effectively performed within 2 months (60 days) after identification of a MUD.

Secondary endpoints

- Graft failure incidence.
- Neutrophils and platelets engraftment at day 100 (first day of 3 consecutive days with neutrophils >0.5 G/L and first day of 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.
- 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, ADV and EBV infection at M12
- Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24
- Non-relapse mortality M24
- Overall survival at M24
- Quality of life questionnaire (PedQQL) at inclusion, post-transplantation, M3, M6, M12, M24
- Chimerism at M1, M3, M6, M12
- 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

Phase II multicenter, national, prospective cohort study.
We use the Simon Minimax Two-Stage Phase 2 design, to demonstrate success (primary outcome) in 70% of patients (to consider treatment as a valuable option) against less than

45% (considered as unacceptable). An interim analysis will be performed after 12 inclusions: the trial will be terminated if 5 or fewer do not receive Upfront MUD HSCT, then the study ends with conclusion of inefficacy. Otherwise, inclusions are pursued until a total of 25 patients. To conclude treatment efficacy, at least 16 successes should be identified among the 25 patients.

Number of participating sites

This is a national multi-center study including all pediatric transplant centres of the SFGM-TC (13 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 after donor identification, in practice 2 months 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).

A specialized consultation in reproductive medicine should be proposed. The recommendations for preservation of fertility are those resulting from the publication of reference (Dalle JH et al, BMT 2017).

1/ Fertility preservation in girls and boys before puberty

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.

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

	Who informs the individual and collects their consent	**When is the individual informed**	**When is the individual's consent collected**
2 parents of the patients. The "Non opposition" of the minor patient should be sought depending on the age of the minor	The transplant physician (investigator of research)	Screening visit	At the inclusion visit

5.2 Baseline visit

At this visit, the consent of the parents will be collected. A Patient Information Sheet and consent form are given to the 2 parents by the investigator. The original version is kept by the investigator and the third copy is kept by the sponsor.
After signing the consent by both parents (and non-opposition of the patient if applicable), the patient 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
- Lansky/Karnofsky performance status assessment
- Complete physical examination
- Echocardiogram with evaluation of shortening fraction
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)" from 5 years old
- 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 (extended phenotyping)
- Chemistry panel (serum electrolytes with creatinine, calcium, glucose, uric acid, magnesium levels, ferritin, CRP)
- Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine)
- Circulating protein electrophoresis
- Pregnancy test (for young women of childbearing age)
- Chimerism markers' identification

The young girl will be considerate as women of childbearing age following menarche, so pregnancy test 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
- Serum PCR for CMV, EBV and ADV

· Imaging :

- Dental radiography
- Total body CT scan
- Chest X ray

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

- Quality of Life

5.3 Follow-up visits post-transplant

Patients will be **monitored daily** during the hospitalization duration, then weekly until day+100 for possible complications related to the procedure or acute GvHD.
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 (v5.0).
- Complete Blood count (every other day), chemistry assessment with kidney and liver test (2/week) will be performed
- Aspergillus antigen, toxoplasmosis according to infection risk, PCR for CMV, EBV, adenovirus will be performed weekly (or more according to clinical context)
- Grading of acute GvHD will be performed weekly during hospitalization and at each visit until D+100, according to MAGIC score (16).

Patients will be assessed (routine follow up) weekly after hospitalization **until D+100 then at M3, M6, M12 and M24** as follow:

- 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 M3, M6, M12, M24).
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood, as well as protide electrophoreris will be performed at D+100, M6, M12, M24.
- Ferritin levels will be recorded at M3, M6, M12, M24
- Chimerism evaluation is performed at D+30, D+100, D+180, M12,
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus will be performed at M1, M2, M3, M6, M12
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC) at M6, M12,
- Safety assessment by collection of all adverse events/serious adverse events at each visit
- Quality of life at post transplantation, 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 for young girl of childbearing age)(before start treatment for conditioning regimen)t)		*D-6*								
Physical examination :disease history, Lansky/Karnofsky performance status assessment,		*x*								
ECG with evaluation of shortening fraction, liver ultrasound & Doppler echography, ultrasound and radiography kidney		*X*						*X*	*X*	*X*
Imaging: *Dental radiography, Total body CT scan, Chest X ray*		*x*								
Pulmonary function test (age>5 years)		*x*						*X*	*X*	
Ferritin level		*x*					*x*	*x*	*x*	*X*
Blood cell count		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Chemistry panel with creatinine, liver test		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
(a) Aspergillus antigen, PCR for CMV, EBV, adenovirus, HHV-6			*x*	*x*	*x*	*x*	*x*	*x*	*x*	
Chimerism (b)		*x*			*x*		*x*	*x*	*x*	
Grading of acute and chronic GvHD				*x*	*x*	*x*	*x*	*x*	*x*	*X*
Immune reconstitution : CD3/CD4/ CD8/ / B lymphocytes (CD19) and NK cells(CD56)							*x*	*x*	*x*	*x*
Quality of life questionnaire (PedQQL))		*x*		*X*			*x*	*x*	*x*	*x*
Adverse events/serious adverse event including severe infections *All toxicity not attributed to GvHD will be classified according to CTC-AE toxicity, v5.0*			*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

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(a) Weekly until D+100: Aspergillus antigen, toxoplasmosis

according to risk of infection, PCR for CMV, EBV, adenovirus

b) On total blood. CD3+ specific chimerism might be of interest in case of total blood mixt chimerism (according to local policy)

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 D+5 post-transplant.
Hospitalizations *-Consultations		No
Imaging	Dental radiography Total Body CT scan Chest X ray	No

*The minimum expected length of hospitalization is 21 days.

TABLE: Indication for volumes authorized to be collected from children participating

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**
0.5-1.5	50-150	1.5-4.5	0.5-1.5
2.5-5	250-500	7.5-15	2.5-5
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 this research, the biological follow up is identical to the current care in allograft.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria of a recipient

Patients:

- age<18 years old

- Pediatric patients aged less than 18 years with idiopathic aplastic anemia and an indication for treatment (severe aplastic anemia or moderate aplastic anemia requiring transfusions)
- With a good probability to have a HLA-10/10 matched unrelated donor available (the patient needs to have at least 3 MUD identified within the book "BMDW (Bone Marrow Donors Worldwide)" or using the easy match software to be included)
- With usual criteria for allo-SCT:
    - Lansky >70% for those below 16 years and Karnofsky > 70% for those above 16 years
    - No severe and uncontrolled infection
    - Adequate organ function: ASAT and ALAT ≤ 5N*, total bilirubin ≤ 2N, creatinine clearance > 70% of higher normal values for age.
- With health insurance coverage (bénéficiaire ou ayant droit)
- Contraception methods** for young girl and men of childbearing age must be prescribed during all the duration of the research.
- Parents having read and understand the information note and signed a written informed consent (the patient's agreement depending on his age will be sought)

*because typical presentation of aplastic anemia post-hepatitis

** 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),
- For man in absence of permanent sterilization: condoms

6.2 Exclusion criteria

Patients:

- With a matched related donor available
- 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
- Renal failure with creatinine clearance below 70% of higher normal for age
- Pregnant (βHCG positive) or breast-feeding
- With Heart failure according to NYHA (II or more)
- Preexisting acute hemorrhagic cystitis
- Urinary tract obstruction
- Yellow fever vaccine within 2 months before transplantation
- With Contraindications to treatments used during the research (see SmPC)*
- Who have any debilitating medical or psychiatric illness, which preclude understanding of the inform consent as well as optimal treatment and follow-up (depending of his age and understanding).

*Available on *ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) or from Vidal.*

6.3 Clinical selection and Inclusion criteria of a donor

Clinical selection of donors must comply with the criteria defined by the decision of 04 November 2014 "fixant les modalités de sélection clinique des donneurs d'organes de tissus et de cellules". In particular:

- HLA-10/10 matched donor will be identified outside the book "BMDW (Bone Marrow Donors Worldwide)" or using the easy match software to be included .At least 3 previously identified donors for each patient enrolled
- The donor aged should be between 18 to 70 years old (or 60 years old for patients sampling in France)

The usual clinical and biological criteria of eligibility of the donors of HSCT will be applied, 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

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6.4 Exclusion criteria of a donor

- 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

6.5 Recruitment procedure

The protocol is carried out by the French reference center for AA and the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) (pediatric centres). Most of the members of SFGM-TC will thus participate to this research. The French biomedicine agency and patients association both support the project. Patients with a good probability to have a 10/10 HLA-MUD identified outside the book will be included in the protocol.

	Number of subjects
Total number of subjects to be included	25
Number of sites	13
Enrolment period (months)	36
Number of subjects/site	1,9
Number of subjects/site/month	0.05

200 new patients with idiopathic aplastic anemia are diagnosed each year with around 30 patients aged less than 18. The chance to find a MUD is about 40% of the patients, which represents 10-15 eligible patients per year.
The same repartition by age group (0-2 years, 2-5 years, 6-9 years, 10-15 years and 15 -18 years) are expected .

6.6 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 will 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 the inclusion period is still ongoing participant will be replaced.

Any data collected prior to the date of premature exit or withdraws consent by the participants may still be used. If a participant exits the study prematurely, and if the participant agrees, the investigator will make every effort to obtain the primary endpoint.

The exit of the study will not affect the usual care of the patient and

The case report form will list the various reasons why the participant has discontinued the study.

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:

- High priority is given to 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 program 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 sponsor (AP-HP) will provide the decision and justification 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.

We use the Simon Minimax Two-Stage Phase 2 design, to demonstrate success (primary outcome) in 70% of patients (to consider treatment as a valuable option) against less than 45% (considered as unacceptable). An interim analysis will be performed after 12 inclusions: the trial will be terminated if 5 or fewer do not receive Upfront MUD HSCT, then the study ends with conclusion of inefficacy. Otherwise, inclusions are pursued until a total of 25 patients. To conclude treatment efficacy, at least 16 successes should be identified among the 25 patients.

7 TRANSPLANT PROCEDURE

7.1 Donor selection

10/10 HLA-MUD (fully matched at the allele level for HLA A, B, C, DRB1 and DQB1)

Creatinine	Dose MTX	Total bilirubin	Dose MTX	Mucositis (a)	Dose MTX
< 15	100 %	< 20	100 %	0	100 %
15-17	75 %	20-30	50 %	1	100 %
18-20	50 %	31-50	25 %	2	50-100 %
> 20	0 %	> 50	0 %	3	0 %

7.2 Transplants modalities

Before to start treatments (D-6), a βHCG test will be done for girl of childbearing age.

7.2.1 Conditioning regimen

The conditioning regimen will depending of the age of the patient:

a) For patients aged less than 14 years: Fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3), and Anti-thymocyte globulin (3.75 mg/Kg/day: day -6 to day -3).
b) For patients aged 14 or more: Fludarabine (30mg/m2/day: day -6 to day -3), cyclophosphamide (30 mg/kg/day: day -6 to day -3), Anti-thymocyte globulin (3.75 mg/Kg/day: day -4 and day -3) and Total Body irradiation 2 gray (day -1).

However, it is allowed to realize TBI before Fludarabine for local planning reasons: TBI day -5, anti-thymocyte globulin D-4 et D-3, Fludarabine D-4 to D-1, cyclophosphamide D-4 to D-1.
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7.2.2 Type of stem cell source

The stem cell source will be **only** bone marrow to avoid an unnecessary higher risk of GvHD is peripheral blood stem cells are sued. The bone marrow collection is carried out according to the practice of each centre with a minimal target dose of $4x10^8$ nucleated cells/kg recipient ideal body weight and infused on day 0, not exceeding the donor volume of 20ml/kg.

However, if the graft is less rich than the minimum target dose, it can be administered at the discretion to the physician.

7.2.3 GVHD prophylaxis

GVHD prophylaxis will consist in the association of cyclosporine plus methotrexate (MTX): IV Cyclosporine 3 mg/kg/j at Day -1 until 1 year post HSCT plus Methotrexate (MTX) IV 10mg/m2 given on day+1, and subsequently at 8 mg/m2 on days +3 and day+6.

Management of treatments:

a) Cyclosporine
Cyclosporin is adapted to the renal function.
It is planned to stop the treatment:
- at M12 (full dose) then a progressive decrease over 3 months post-SCT
- in case of renal failure (<30 ml/min) or thrombotic microangiopathy

b) Methotrexate

In case of renal failure, hepatic failure or severe mucositis, the dose will be adapted as follow:

(a) according to Graft scale of Bearman.

7.2.4 Prevention of EBV reactivation (Investigational Medicinal Product, cf. 8.1)

All patients will received 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m2) at Day+5 to prevent Epstein-Barr virus (EBV) reactivation (day+5) (14).
Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before administration of Rituximab.

7.2.5 Infection Prophylaxis

Prophylactic and curative anti-infectious treatments (antibiotics, antivirals, antifungals) will be administered according to the ECIL recommendations (link: www.kobe.fr/ecil workshops, recommendations).
- Prevention of fungal infections:by azols according to ECIL5, adapted to the SCT risk group
- Prevention of HHSV and VZV reactivation: acyclovir 250mg/m2 X3/day iv then Valaciclovir: 500mg /day po
- Prevention of toxoplasmosis reactivations and pneumocystis: Bactrim 800mg X3/week or Atovaquone 750 mg x 2/day in case of cytopenias after engraftment
- Prevention of encapsulated bacteria: Oracilline 50 000 UI/kg x 2/day.
- Monthly polyvalent immunoglobulins if hypogammaglobulinemia (<4 g/L)

❖ Management of toxicities:

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- 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 and therapeutic drug monitoring,.Cymevan to cytopenias. These adaptations will be regularly carried out in the transplantation department.

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

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

7.3.1 Authorized treatments

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

7.3.2 Treatments forbidden

Live attenuated vaccines (Yellow fever vaccine, Mumps-Measles-Rubella vaccine, ….) are contraindicated in HSCT patients up to 24 months post-HSCT.

7.3.3 Treatments not recommended

- <u>For cyclophosphamide</u>
  - Attenuated vaccine (except yellow fever who is forbidden during 6 months after treatment discontinuation, *see paragraph above*)

- Phenytoin
- Pentostatin

- For Fludarabine
  - Pentostatine
  - Dipyridamole or other inhibitor of adenoside captation

- For anti-thymocyte globulin
  No recommendation
- For Methotexate
  - Ciprofloxacine
  - Nonsteroidal anti-inflammatory drugs
  - Cytarabine
  - Furosemide
  - Probenecid
  - Oral antibiotics
  - Mercaptopurine
  - Theophylline
  - Hepatotoxic products
  - Vitamin

Patients receiving, Benzodiazepines, Carbamazepine, Corticosteroids, Chloral hydrate, Phenobarbital Rifampicin, should be closely monitored for signs of toxicity
With the exception of the drugs listed above, the other drugs in reference with their SPC and "associations to be considered" will be administered according to the usual practice of the centre and at the discretion of the investigator.

7.3.4 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 centre for aplastic anemia.

8 ADDITIONAL MEDICINAL PRODUCTS TO TRANSPLANT PROCEDURE SUPPLIED BY THE SPONSOR

8.1 Rituximab

Posology for clinical trial: Rituximab will be given in one injection (150 mg/m²) 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 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 administration of Rituximab. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, 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.

Traceability information and monitoring compliance for the Rituximab :The unique injection will be recorded on a specific traceability document.

9 EFFICACY ASSESSMENT

9.1 Description of efficacy endpoints assessment parameters

9.1.1 Effective date of MUD-HSCT

The primary endpoint is defined by an upfront MUD HSCT effectively performed within 2 months (60 days) after identification of a MUD.

9.1.2 Progression-free survival

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

9.1.3 Acute GvHD

Acute GvHD is defined according to MAGIC CONSORTIUM 2016 criteria (16). 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 2015 (17). 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).

9.2 Anticipated methods and timetable for measuring, collecting and analyzing 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 Jean-Hugues Dalle, Pr Régis Peffault de Latour, Pr Matthieu Resche-Rigon and for the DRCD: Project manager and Clinical Research Assistant.

10.2 Data Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

A DSMB will be convened for this biomedical research. The DSMB will hold its preliminary meeting before the first inclusion of the first subject.
All missions as well as the precise operating methods of the DSMB are described in the charter for the research's DSMB.
The members are : Dr Edouard Forcade (CH Bordeaux), Dr Raynier Deviller (Institut Paoli Calmettes, Marseille), Pr Michel Duval et Pr Aline Fersters

<u>General information about the DSMB</u>
The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and one specialist in the medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

The DSMB must hold its preliminary meeting before the first inclusions of the first subject and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

Definition of the DSMB's missions:

- Validation of the research methodology: The proposed methodology for the clinical trial will be validated by the DSMB so that it does not jeopardise the safety of subjects, in particular relating to the inclusion and randomisation methods.
- Validation of tolerance monitoring methods:
  - nature of the evaluated parameters
  - frequency of the evaluations, consultation schedule
- Validation of termination criteria:
  - criteria for terminating a subject's participation for tolerance reasons
  - criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:
  - In light of the interim analyses of the primary enpont if one arm seems to be clearly in defavour of patients
  - In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

Definition of the DSMB's operating methods:
Meetings modalities (open session, then closed sessions) and frequency will be detailed in the DSMB charter at the latest before inclusion of the first patient,
Modalities and format expected for the transmission of SAE from the sponsor to the DSMB will be detailed in the DSMB charter at the latest before inclusion of the first patient,
The sponsor retains decision-making authority. The sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and when applicable to the CPP.

11 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

11.1 Description of Safety endpoints assessment parameters

Collecting all adverse events that occur during the research will ensure safety assessment. 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 (15).

The expected incidence of grade 2-4 acute GvH is around 40-45% as in all allograft protocols, the incidence of severe acute grade 3-4 GvH of the order of 15-20% and the incidence of chronic GvH < 10%.
With regard to fertility, the risk of subfertility is low with the conditioning of children under 14 and not high for those over 14. Indeed, the cumulative toxic dose to the gonads for cyclophosphamide is of the order of 9 to 12 g//m². Here the cumulative dose is 120mg / kg or about 3.6g / m² so well below the dose deemed toxic. With regard to conditioning comprising an TBI 2Gy, this dose was described in a single animal publication as likely to be the IC50 dose to the ovaries but has since been contradicted and it is likely that the toxic dose to the ovaries as to the testicles is rather of the order of 6Gy.
The risk of EBV reactivation is low since we are addressing a young population that is most often EBV negative, however a systematic injection of Rituximab is planned on D+5. In the end, the reactivation rate is difficult to predict but probably < 10%.

The risk of infection is always present in allogeneic hematopoietic stem cell transplantation due to neutropenia induced by conditioning and prolonged drug immunosuppression for 9-12 months in the case of transplants for non-malignant pathologies. However, the particularity here is to address patients treated for aplastic anemia. The reference treatment is, as described in the rationale for the study, a combination of horse anti-lymphocyte serum and ciclosporine (+ a few days of corticosteroids) with a duration of drug immunosuppression (IST) rather of the order of 18 to 36 months. Overall, the median duration of neutropenia expected post-allograft is shorter than the median duration expected after treatment with SAL-CSA and the duration of IST is also shorter in the case of allograft.

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

Adverse events shall be collected according to the schedule in table of paragraph 4.5 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 (AE)**

AE is defined by 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 reaction is defined for a medical occurrence 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 due 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 hospitalization or prolongs existing hospitalization, 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.
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

The 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 the study procedures**.**

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 1º of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

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 inpatient 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)
  -Veno-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
  - Severe dyspnoea, bronchospasm or hypoxia related to Rituximab
- 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 adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

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 for serious adverse events (see 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.

- *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).

The investigator must complete each item 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 non-identifying. 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 notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs
- 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 if the product is not authorised, 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, anti-thymocyte globulin, ciclosporin, methotrexate, rituximab and drugs used for premedication (reference to latest version available on http://base-donnees-publique.medicaments.gouv.fr).

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 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 involved about any information that could adversely affect the safety of the research participants.

11.3.1.6 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. (see also "Emerging safety issue")

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 the first participant.

12 DATA MANAGEMENT

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

12.2 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.

12.3 Data processing and storage of research documents and data

Data entry

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

12.4 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

12.1 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

The optimal two-stage design to test the null hypothesis that P ≤ 0,450 versus the alternative that P ≥ 0,700 has an expected sample size of 18.15 and a probability of early termination of 0,527. If the strategy is actually not effective, there is a 0,043 probability of concluding that it is (the target for this value was 0,050). If the strategy is actually effective, there is a 0,196 probability of concluding that it is not (the target for this value was 0,200). After testing the strategy on 12 patients in the first stage, the trial will be terminated if 5 or fewer respond. If the trial goes on to the second stage, a total of 25 patients will be studied. If the total number HSCT is less than or equal to 15, the strategy is rejected.

Analysis of Secondary Endpoints

- Graft failure incidence will be estimated with its exact 95% CI
- Incidence of neutrophils and platelets engraftment at day 100 with their exact 95% CI will be estimated using Gray's estimator. Death without neutrophils and platelets engraftment will be considered as competing events respectively.
- Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions will be summarized by their median and interquartile range
- Acute GvHD incidence at month 3 (M3) with its exact 95% CI will be estimated using Gray's estimator. Death without acute GvHD will be considered as competing event.
- Chronic GvHD incidence with its exact 95% CI will be estimated using Gray's estimator. Death without Chronic GvHD will be considered as competing event.
- Relapse incidence at M12 and M24 will be estimated using Gray's estimator. Death without relapse will be considered as competing event.
- Progression free survival at M12 and M24 will be estimated with its 95% CI using Kaplan Meier estimator
- Incidence of CMV and EBV infection at M12 will be estimated with its exact 95%CI confidence interval.
- Severe infections incidence (CTAE grade 3-4) at M3, M6, M12 and M24 will be estimated using Gray's estimator. Death without infection will be considered as competing event.
- Non-relapse mortality M24 will be estimated using Gray's estimator. Relapse will be considered as competing event.
- Overall survival at M24 will be estimated with its 95% CI using Kaplan Meier estimator
- Quality of life questionnaire (PedQQL) at inclusion, post-transplantation, M3, M6, M12, M24 will be summarized by their median and interquartile range
- Chimerism at M1, M3, M6, M12, will be described.

- 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 summarized by their median and interquartile range
- Ferritin levels at M3, M6, M12, M24 will be described using median and interquartile range.

Analysis of Safety
Safety analyses will involve examination of the incidence, severity, and type of treatment adverse events reported, changes in vital signs and laboratory test results from baseline, and concomitant medications use.

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

The optimal two-stage design to test the null hypothesis that P ≤ 0,450 versus the alternative that P ≥ 0,700 has an expected sample size of 18.15 and a probability of early termination of 0,527. If the strategy is actually not effective, there is a 0,043 probability of concluding that it is (the target for this value was 0,050). If the strategy is actually effective, there is a 0,196 probability of concluding that it is not (the target for this value was 0,200). After testing the strategy on 12 patients in the first stage, the trial will be terminated if 5 or fewer respond. If the trial goes on to the second stage, a total of 25 patients will be studied. If the total number HSCT is less than or equal to 15, the strategy is rejected.

13.3 Anticipated level of statistical significance

The type I error will be set at 0.05.

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

All the effort will be done to avoid missing data in the outcomes. All causes of study dropouts will consider the patients as failures.
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.

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

All modifications of the initial plan will be submitted to the scientific committee, the investigator and the sponsor.

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.

14.7 Pharmacist's commitment of responsibility

Treatments will be centralized at DEC-AGEPS (ageps.aphp.fr/).

DEC-AGEPS will:

- Purchase the experimental treatment (rituximab) according to the rule of public market purchase
- Handle, repackaking, labelling of boxes
- Dispatch experimental products to local pharmacies
- Preparation all documents related to the experimental treatments' purchase, dispatching, transport, return and destruction

Local hospital pharmacies will store and dispense patient treatment to care givers, and will destroy remaining investigational drugs, with respect to good practices and to the pharmacy manual..

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 Authorization 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

If PHRC: "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 NCT05419843

18 BIBLIOGRAPHY

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19 LIST OF ADDENDA

19.1 List of investigators

1	Dalle	Jean-Hugues	jean-hugues.dalle@aphp.fr	APHP	Hôpital Robert-Debré
2	Peffault de Latour	Régis	regis.peffaultdelatour@aphp.fr	APHP	Hôpital Saint-Louis
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11	Bruno	Bénédicte	Benedicte.bruno@CHRU-LILLE.FR	CHU Lille	Hôpital Jeanne de Flande
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13	Buchbinder	Nimrod	Nimrod.Buchbinder@chu-rouen.fr	CHU Rouen	Hôpital Charles Nicolle

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 un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

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

Il est 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 : **UP FRONT MUD**

Code de la Recherche : APHP 200005

Risque : D

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

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

Titre complet de la recherche :
Up-front Matched Unrelated Donor Transplantation in Pediatric Patients with Idiopathic Aplastic Anemia: a phase II feasibility 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)

Sexe : ☐ M ☐ F

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

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

Age : |__|__|__|ans

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

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

Date de la greffe : |__|__| |__|__| |__|__|__|__|

Ou non réalisée : ☐

Conditionnement de la greffe : Conforme au protocole oui ☐ non ☐
Si non : indiquer la modification
.....

Source de cellules : Moelle Osseuse : oui ☐ non ☐,si non précise
.....

Nombre de cellules administrées : Conforme : oui ☐ non ☐,si n
préciser : .....

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

4. Médicament non experimental 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	D+5 post-HSCT : |__|__| |__|__| |_2_|_0_|__|__|

Acronyme : **UPFRONT-MUD**

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

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

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

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

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

6. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire

.....

<u>Date de survenue des premiers symptômes</u> : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels : .....

<u>Organe(s) concerné(s)</u> :

.....

<u>Date d'apparition</u> de l'EIG :

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

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

☐ *donnée manquante*

<u>Degré de sévérité</u>

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

<u>Critères de gravité</u> :

☐ 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 :

- 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_|__|__|

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : **Erreur ! Source du renvoi introuvable.**

Acronyme : **UPFRONT-MUD**

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, notamment le compte-rendu opératoire, le comp d'hospitalisation, les résultats du chimérisme, résultat d'autopsie en cas de décès...]**
.....
.....

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 (prévention réactivation EBV)**
☐ **à la prophylaxie de la GVHD (préciser le(s) médicament(s)) :** .....

Non lié à la recherche :
☐ **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

Délégation à la Recherche Clinique et à l'Innovation (DRCI)	***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 : **UP FRONT MUD**

Code de la Recherche : APHP 200005

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

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|__|__|

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|__|__|

Expositions au cours de la grossesse :

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

Autre (préciser) :

4. Antécédents maternels

Médicaux :

Chirurgicaux :

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

5. 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

6. 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)

7. 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)* :

8. 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

9. 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 SmPC or Investigator's Brochure *(*separate documents*)*

19.5 Include the SCP

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

19.6 Questionnaire or scale

1-Quality of life questionnaires

questionnaire PedsQL Enfant (separate documents)

2- Scale

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

version 5.0

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Acute GVH according to MAGIC CONSORTIUM 2016

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

1. **Stade par organe**

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

SC=surface corporelle

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

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

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

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

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

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

Manifestation de la GVHD chronique

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

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

Manifestation de GVHD chronique

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

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

Ongles Onychodystrophie, onycholyse, striés, fendus.

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

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

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

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

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

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

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

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

Muscles Faiblesse proximale, crampes.

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

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

Gradation de GVHD chronique par organe:

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

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