Reduced Toxicity Conditioning prior to Unrelated Cord Cell Transplantation for high risk myeloid malignancies
TBF-Cord

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par l'investigateur COORDONNATEUR et le représentant du PROMOTEUR

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Titre : Reduced toxicity conditioning prior to unrelated cord cell transplantation for high risk myeloid malignancies (TBF-Cord)

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L'investigateur coordonnateur :

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Glossary of Abbreviations

AE	Adverse event
Allo-HSCT	Allogeneic haematopoïetic Stem Cell Transplantation
AML	Acute Myeloid Leukaemia
BM	Bone Marrow
CR	Complete response
CRF	Case report form
CSA	Cyclosporine A
CTC	Common toxicity criteria
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
GCP	Good clinical practice
G-CSF	Granulocyte - colony stimulating factor
GVHD	Graft Versus Host Disease
ICH	International Conference on Harmonization
DFS	Disease-free Survival
MedDRA	Medical Dictionary for Regulatory Activity
MUD	Matched Unrelated Donor
NCI	National Cancer Institute
NRM	Non relapse Mortality
OS	Overall Survival
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cell
RI	Relapse Incidence
RIC	Reduced Intensity Conditioning
SAE	Serious adverse event

1. SYNOPSIS

Allogeneic cord blood stem cell transplantation is a potentially curative therapy for patients with haematological malignancies. We have extensive experience with the use of cord blood transplantation (CBT) in patients with advanced myeloid malignancies. In adults however, the 40% non-relapse mortality (NRM) rate observed after CBT conditioned with a myeloablative conditioning has encouraged the development of CBT with reduced intensity conditioning (RIC). Our previous national CBT protocol (the Minicord French protocol - NCT00797758) showed that RIC CBT can reduce NRM, but relapse remains the main post-transplant event (>30% at one year). Thus, the development of reduced toxicity rather than RIC conditioning for CBT is warranted in order to improve the outcome of such transplants by limiting NRM and reducing relapse rate. The Fludarabine, ATG and intensified doses of IV Busulfan (9.6 mg/Kg total dose) regimen is a well-established preparative regimen for reduced-intensity/toxicity conditioning prior to allogeneic stem cell transplantation using peripheral blood stem cells mobilized with G-CSF (ClinicalTrials.gov Identifier: NCT00841724). However, such regimen is likely not sufficient to allow for CB cell engraftment. Thiotepa is an alkylating and radio-mimetic agent with a large anti-tumor activity including leukemic cells, the ability to cross the blood-brain barrier and to improve engraftment of hematopoietic stem cells. This drug has been combined to usual conditioning regimen without increasing the toxicity but improving the engraftment rate and potentially reducing the relapse rate. Thus, in the context of adult CBT for high risk myeloid malignancies, we propose to prospectively evaluate a reduced toxicity conditioning based on the association of Thiotepa, Fludarabine, IV Busulfan and ATG with the objective to achieve acceptable NRM rates, and to allow for improved anti-leukemic control based on the cytotoxic component of the conditioning regimen itself, while waiting for the long term immune-mediated disease control (GVL effect).

Objectives of the clinical research:

The primary objective is to determine the safety and efficacy of a pre-transplant reduced toxicity conditioning regimen (thiotepa, busulfan, fludarabine and ATG) followed by unrelated cord blood allogeneic stem cell transplant for high risk myeloïd malignancies.

Secondary objectives will be to evaluate the following items:

- Incidence of engraftment after transplantation
- Incidence and severity of acute graft-versus-host-disease (GVHD)
- Incidence and severity of chronic GVHD
- Rate of disease relapse at one year after transplantation
- Quality of life
- Immune recovery of peripheral blood lymphocyte subsets (B, NK, T CD4, T CD8, T regs, iNKT, dendritic cells) and analysis of KIR mismatches between patient and cord blood units

Main endpoint :

Non relapse mortality at 12 months after transplant

Secondary endpoints :

-Cumulative incidence of engraftment
-Cumulative incidences of acute and chronic GVHD
-Disease-free survival at one year after transplantation

-Overall Survival at one year after transplantation
-Evaluation of quality of life: FACT-BMT (version 4.0)

Experimental plan :
Multicenter single stage A'Hern phase II trial

Main inclusion criteria:
Patients diagnosed with:

- Acute myeloid leukemia (AML) past first remission or CR1 with high risk features
- -or Myelodysplastic syndrome with International Prognostic Scoring System score ≥ 2

Absence of a matched sibling or unrelated available donor (HLA 10/10 or 9/10 with mismatch on HLA Cw, based on each center's donor selection criteria)
Cord blood units must match patient at 4, 5, or 6/6 HLA class I serological & II molecular antigens with a minimum of 4 x 10^7 TNC/kg (with a minimum of 2.5x10^7 TNC/kg per cord blood unit in case of 2 cord blood units) of recipient body weight in the pre-thawed fraction.
Age ≥ 18 and ≤ 65 years.
Cardiac function - LVEF ≥ 45%.
Pulmonary function - diffusion capacity of at least 50% predicted.
Creatinine clearance ≥ 50 ml/min.
SGPT ≤ 4x normal , serum bilirubin < 2 x normal.
Written informed consent.

Main exclusion criteria:
Pregnant women.
Positive HIV serology
Active CNS leukemia
Chronic or active Hepatitis B or Hepatitis C.

Proposed Treatment/Study Plan:
Thiotepa 5 mg/Kg/day for 2 days (D-7 and D-6)
Fludarabine 40 mg/m²/day for 4 days (D-5 to D-2)
Busulfan IV 3.2 mg/Kg/day for 3 days (D-5, D-4 and D-3)
Thymoglobuline 2.5 mg/Kg/day for two days (D-3 and D-2)
GVHD prophylaxis: Cyclosporine and mycophenolate Mofetil
GCSF daily after Day 7 post-HSCT until granulocyte recovery

Statistical Plan:
Based on results from the literature, the hypothesis for the primary endpoint is an improvement in non-relapse mortality at one year after transplantation from 35% to 20%. Using a one step A'Hern procedure (Statist. Med. 2001; 20:859-866), 55 patients are needed. In all, 57 patients will be included (taking into account that after registration, there is a risk of dropout i.e. a patient who will not receive a transplant due to rapidly progressive disease, infection or other events occurring after planning the transplant, but before start of conditioning). If the number of patients dying of NRM at

one year is 13 or less, the hypothesis that NRM ≥ 0.35 is rejected with a target error rate of 0.050 and an actual error rate of 0.049. If the number of patients dying of NRM at one year is 13 or less, the hypothesis that NRM ≤ 0.20 is rejected with a target error rate of 0.20 and an actual error rate of 0.197.

Patients' follow-up:
Clinical and biological endpoints will be assessed at baseline and then at day 30, day 100, 6, 12 months post-transplant and at the end of the study.
In addition to usual clinical and biological evaluation criteria, we plan to perform blood collection
Post-transplant immune reconstitution will be analyzed at inclusion and at day 30, day 60, day 100, 6 and 12 months post-transplantation. At each time point, 40 ml of blood will be sent from each associated team to the investigator's central collection laboratory.

Duration of participation for each patient:
Study duration: 36 months
Recruitment duration: 24 months
Duration per patient: 12 to 36 months, depending on the time on enrolment.

2. BACKGROUND

2.1 Experience of cord blood transplant after myeloablative conditioning in adults

Unrelated cord blood transplantation (CBT) has been shown to be a suitable alternative source of hematopoietic stem cells for adults with haematological malignancies and particularly acute myeloid leukemias (AML) in the absence of an HLA-matched donor [1-3]. The two year overall and leukaemia free survivals were similar between CBT and allogeneic bone marrow transplants (BMT) in the first retrospective comparative study published by Rocha et al. (OS 36 % with CBT versus 42 % with BMT, p=0.08 and LFS 33% with CBT versus 38% with BMT, p=0.06) [1]. Despite the use of cord blood units presenting 1 or 2 HLA mismatches with the recipient, incidence of acute and chronic GvHD was not increased with CBT as compared to conventional bone marrow or peripheral blood stem cells transplants [1,3]. In the retrospective study of Rocha et al. the relative risk of developing acute GVHD was reduced with CBT as compared to BMT (RR =0.57, 95% CI =0.37-0.87, p= 0.01), and a trend towards a reduced risk of chronic GVHD was observed (RR=0.64, 95% CI 0.37-1.1, p=0.11) [1].
However, because of delayed engraftment and immune T cell reconstitution leading to increased infections, non-relapse mortality at one year following myeloablative conditioned CBT in adults remains unacceptably high from 30 to 45% [1-3]. Engraftment failure occurred in 10 to 20% of CBT and was significantly related to the cryopreserved total nucleated cells (TNC) contained in the graft [1,2]. A minimum of $3x10^7$ TNC/kg in one or two cord blood units is therefore recommended. Relapse incidence from 22 to 30 % at two years is comparable between CBT and bone marrow transplants [1-3]. Two years overall survival is reported from 33 to 43% [1-3]. This results were recently confirmed in a larger series of patients transplanted using CB or PBSC or BM after MAC regimen and reported from CIBMTR and Eurocord/EBMT [4].

Thus, although the results of CBT after myeloablative conditioning in adults have shown the feasibility of the transplant procedure, the 40% NRM of the procedure remains a major limiting factor in for the population of adult AML/MDS patients.

2.2 Experience of reduced intensity conditioned cord blood transplants (RIC CBT) in adults

Over the past decade, reduced-intensity conditioning (RIC) regimens have become a well-established approach in adult patients, offering curative allogeneic hematopoietic stem cell therapy to older persons and patients with comorbidities, rendering them otherwise ineligible for myeloablative procedures [5]. In adult CBT, the use of RIC regimen has been developed in order to overcome the high toxicity of CBT with MAC regimens and to transplant older patients with comorbidities. Several Fludarabine-based conditioning has been described allowing successful engraftment of CBT (reviewed by Cutler 6, Table 1).

The largest experience of RIC for CBT in adult AML comes from the Flu-Cy-TBI (Fludarabine 200 mg/kg-Cyclophosphamide 50 mg/kg-200 cGy TBI) regimen first described by the group of Minnesota [7-9]. Results of two phase II CBT clinical trials using this regimen mainly in AML patients has been recently reported, the French multicenter Minicord (n=65) [10] and the American BMT CTN 0604 (n=50) 11. Non relapse mortality, relapse incidence, disease free survival and overall survival at one year were 18% (95% CI: 11–36%), 30% (95% CI: 19–42%), 52% (95% CI: 41–66%) and 60% (95% CI: 48–74%) in the Minicord trial and 24% (95% CI: 8–28%) , 31% (95% CI: 17–44%), 46% (95% CI: 31–60%) and 54% (95% CI: 38–67%) in the American protocol, respectively. The most cause of death was disease relapse in both trials. Recently, a retrospective study from the CIBMTR reported comparable final outcome for patients receiving double CBT

using Flu-Cy-TBI or other RIC as compared to patients having received a RIC with PBSC from unrelated donors [11].

If these studies have shown the reduced toxicity of RIC regimens for CBT in adults, further improvements are needed to reduce the risk of relapse.

Table 1 Summary of published RIC umbilical cord blood studies

Author	*Sample size*	*Conditioning regimen*	*No. of cord blood units infused*	*Median TNC count (per kg)*	*Median $CD34^+$ cell count (per kg)*	*Incidence, median time to neutrophil recovery*	*Incidence, median time to plt recovery*	*TRM at 100 days (%)*	*1-Year survival (%)*
Cutler[4]	53	Flu 30 mg/m^2 × 6 Mel 80 mg/m^2 × 1 ATG 1.5 mg/kg × 6	2	5.16×10^7	12.54×10^6	92.5%, 20 days	86.8%, 41 days	13.2	71.2
Uchida[27b]	70	Flu 125–180 mg/m^2 total Mel 80 mg/kg × 1 TBI 4 Gy (n = 65/70)	1	2.810^7	0.84×10^5	79%, 18 days	63%, 35 days	43	23 at 2 years
Brunstein[2]	110	Cy 50 mg/kg × 1 Flu 40 mg/m^2 × 5 TBI 200 cGy × 1	2 (n = 93) 1 (n = 17)	3.7×10^7 3.3×10^7	4.9×10^5 3.8×10^5	92%, 12 days	65%, 49 days	19 (day 180)	45 at 3 years
Miyakoshi[30]	34	Flu 25 mg/m^2 × 5 Mel 80 mg/m^2 × 1 TBI 4 Gy	1	2.4×10^7	NA	91%, 20 days	79%, 38 days	11.8	70
Komatsu[16]	17	Flu 30 mg/m^2 × 6 Bu 4 mg/kg × 2	1	2.6×10^7	0.74×10^5	53%, 18 days	NA	12	35[a]
Misawa[6]	12	Flu 200 mg/m^2 Cy 50 mg/kg × 1 TBI 3 Gy	1	2.55×10^7	0.91×10^5	91%, 17 days	42%, 32 days	42	50
Mancías-Guerra[17]	11[d]	Bu 4 mg/kg × 2 Cy 350 mg/m^2 × 3 Flu 30 mg/m^2 × 3	1	NA	0.7×10^5	24 days	26 days	27[d]	63.6[d]
Kishi[28c]	57	Flu 25 mg/m^2 × 5 Mel 80 mg/m^2 × 1 TBI 4 Gy	1	NA	2.9×10^5	79%, 19 days	NA	62 (day 180)	NA
Miyakoshi[18]	30	Flu 25 mg/m^2 × 5 Mel 80 mg/m^2 × 1 TBI 4 Gy	1	3.1×10^7	0.74×10^5	87%, 17.5 days	40%, 39 days	27	32.7
Chao[29]	13	Flu 30 mg/m^2 × 4 Cy 500 mg/m^2 × 4 Horse ATG 30 mg/kg × 3	1	2.1×10^7	1.3×10^5	12 days[e]	14 days[e]	15	43
Rizzieri[5]	2	Flu 30 mg/m^2 × 4 Cy 500 mg/m^2 × 4 Horse ATG 30 mg/kg × 3	1	6.5×10^7 2.9×10^7	3.7×10^5 1.0×10^5	10 and 30 days	NA	0	100

Abbreviations: ATG = anti-thymocyte globulin; Flu = fludarabine; Mel = melphalan; NA = not available; RIC = reduced-intensity conditioning; TNC = total nucleated cell; TRM = treatment related mortality.
[a]Estimated from the literature.
[b]Includes patients from the study of Miyakoshi *et al.*[18] and Kishi *et al.*[28] This series was limited to patients > 55 years.
[c]Includes patients from the study of Miyakoshi *et al.*[18]
[d]Only adult patients included.
[e]Excludes patients without nadir.

2.3 Rationale for the use of a reduced intensity/toxicity conditioning regimen based on Fludarabine and 3 days of Busulfan IV in adult AML patients

Reduced intensity conditioning regimens associating Fludarabine, ATG and 2 days of IV Busulfan (6.4 mg/kg) have been reported to be well tolerated in adult patients but the relapse rate above 30% in high risk AML /MDS remained an issue leading to long term survival of about 40 % of the patients [12,13]. Reduced intensity/toxicity regimens based on the association of Fludarabine and 3 days of Busulfan IV (Busilvex 9.6 mg/kg) (FB3) have been developed in order to reduce the relapse

rate without significantly increasing the non-relapse mortality. The english experience, reported by Richardson and Ochard at the 2011 EBMT congress with a FB3-Campath regimen in 42 patients with very high risk myeloid and lymphoid malignancies, showed promising results with 7% of non-relapse mortality at 3 months and 52% overall survival at 2 years. Dr Reman reported preliminary results with a FB3-ATG regimen in 19 patients allografted for several high risk haematological malignancies confirming the low non-relapse mortality (10%) of this regimen and a low relapse rate although the follow up was limited to 17 months (Reman et al., BMT 2011, Abstract P977). The latest regimen has been recently explored in a multicentre French study conducted by Pr D. Blaise and M. Mohty in 80 patients (ClinicalTrials.gov Identifier: NCT00841724). Preliminary results have been presented at last EBMT meeting (Mohty et al, EBMT 2013, Abstract O376). At 2 years the NRM was 11% (95% CI C5.5-19%) and the OS was 62% (95% CI 51-73%).

The FB3 conditioning regimen represents a good candidate platform of RTC for adult AML patients.

2.4 Engraftment issues with RIC CBT

Engraftment failure remains an issue after CBT in 15 to 20% of cases after MAC 1,2. All RIC regimens do not allow successful engraftment (reviewed by Cutler 6, table 1). Non-TBI, non-ATG conditioning regimens with Fludarabine and Melphalan or even more myeloablative doses of busulfan were not sufficient to promote sufficient immunosuppression to allow engraftment in about 50% of CBT recipients [14,15]. In the other side, it has been reported in animal models that the injury associated with the intensity of the conditioning upregulates SDF-1α out of the bone marrow, which results in the retention of CXCR4+ haematopoietic progenitors in non-marrow spaces and impairs engraftment [16].

The use of reduced intensity/toxicity conditionings certainly requires the association to some immunosupressive and marrow necrotic factors such as ATG, TBI or other radiomimetic drugs like Thiotepa, to ensure the engraftment of cord blood stem cells.

2.5 Rationale for using Thiotepa in the conditioning

Thiotepa is a polyfunctional cytotoxic agent related chemically and pharmacologically to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylene imine radicals that, as in the case of irradiation therapy, disrupt the bonds of DNA, e.g. by alkylation of guanine at the N-7, breaking the linkage between the purine base and the sugar and liberating alkylated guanine. Thiotepa is efficient on a large spectrum of tumor cells including haematological malignancies.
Its main limiting toxicity is myeloablation at doses above 180 mg/m^2. As an alkylating agent, and due to its lack of extramedullary toxicity despite dose escalation beyond myelotoxic doses, Thiotepa has been used (at the dose of 10 to 20 mg/kg) for decades in combination with other chemotherapy drugs prior to autologous and allogeneic stem cell transplantation without increasing the non-relapse toxicity even in association with myeloablative conditioning regimens.
In addition, in association to total body irradiation in mice, Thiotepa has been shown to improve the engraftment of allogeneic bone marrow stem cells because of myeloablative/necrotic but also immunosuppressive properties [17]. Similar results have been observed in humans, including in T cell depleted haematopoietic stem cell transplantation [18].

According to these well-established characteristics, Thiotepa represents a good candidate drug for strengthening engraftment, improving disease control without increasing the toxicity of the conditioning regimen in CBT.

2.6 Experience with the use of thiotepa in the conditioning of CBT

Thiotepa, at the dose of 5 mg/kg/day for 2 days (10 mg/kg), has been used in the conditioning regimen of CBT, firstly by the group of Pr Sanz in Spain, in addition to oral Busulfan 4 mg/kg/day for 3 days (12 mg/kg, equivalent 9.6 mg/kg of iv Busulfan), Cyclophosphamide 60 mg/kg/day for 2 days (120 mg/kg) in the 21 first patients or Fludarabine 30 mg/m2/day for 5 days (150 mg/m2) and anti-thymocyte globulin (ATG): Lymphoglobuline (15 mg/kg/day for 4 days) or Thymoglobuline (4 to 8 mg/kg) in high risk AML and CML adult patients [19,20]. Reported myeloid engraftment rates were above 88%, essentially depending on the numbers of infused $CD34^+$ cell doses (improved over $1.5x10^5$ CD34/kg). NRM remained relatively high in the total group of patients (39% at 2 years in the AML population) depending on the intensity of the conditioning (increased with the use of cyclophosphamide in comparison to Fludarabine), the dose of ATG (increased infectious risk with 8 mg/kg as compared to 4 mg/kg of Thymoglobuline), the dose of $CD34^+$ cells and disease status at transplant. The CI of relapse at two years was 19% in a group of 49 patients transplanted for AML [20].

More recently, the same group has reported their experience of Thiotepa associated with a FB3 (TBF) and ATG regimen (Thiotepa 5 mg/kg/day for 2 days, iv Busulfan 9.6 mg/kg in 3 days, Fludarabine 50 mg/m2/day for 3 days, rabbit ATG Thymoglobuline 2 mg/kg/day for 4 days) and the use of one cord blood unit in a heterogeneous group of 88 paediatric and adult patients allografted for several haematological malignancies (AML, ALL, MDS and lymphomas) [21].The CI of myeloid engraftment at 44 days was 94%. The CI of NRM at 100 days and at 5 years was 14% and 44%, respectively. The 5 years CI of relapse was 18%. Similar outcomes have been reported by another group with CBT conditioned with Thiotepa 10 mg/kg, Fludarabine 160 mg/m^2, Melphalan 140 mg/m^2 and rabbit ATG 3 mg/kg [22].

A recent analysis from the Eurocord registry on 239 patients transplanted for acute leukemia in CR1 showed that the TBF-based conditioning regimen for adult CBT allowed a probability of 46+/-6 % of LFS and 18+/-3 % of relapse incidence at 2 years, which accounts for one of the best regimen of the registry. Outcomes of single CBT using TBF-regimen were indeed comparable to those of double UCBT using the Minnesota myeloablative CBT regimen (with 12 Gy TBI) and superior to those of other single CBT receiving different MAC (Ruggeri et al., Leukemia 2014).

However, all these studies have been performed retrospectively and in heterogeneous groups of patients. The TBF and ATG-based regimen for CBT has never been tested or validated in a prospective multicentre fashion.

We thus propose to prospectively analysed the clinical results of a modified so-called "reduced toxicity conditioning" regimen based on the combination of IV Busulfan (9.6 mg/kg), Fludarabine (160 mg/m2), Thiotepa (10 mg/kg) and rabbit ATG (Thymoglobuline 5 mg/kg) with the aim to deliver a relatively high dose of myeloablation that would allow optimal disease control and engraftment while minimizing toxicity in a homogeneous cohort of high risk AML and MDS adult patients.

This study would be the first multicentre prospective study evaluating the efficacy and safety of a RTC in adult CBT for high risk myeloid malignancies.

4.

2.7 Risk/Benefit assessment

5. 2.7.1 Benefits:

2.7.1.1 ***Individual benefit:***

The expected individual benefit of the transplant procedure is a prolonged survival of their disease as compared to non-transplanted patients.

2.7.1.2 ***Collective benefit:***

The expected collective benefit is a reduced risk of relapse at one year in patients treated for AML and MDS. Thus, one can expect a prolonged overall survival of this population and reduced medical costs.

6. 2.7.2 Risks

2.7.2.1 Individual risks

Physical risks:

They are related to the disease and the transplant toxicity.

Risks related to the disease:

-infections due to neutropenia, frequent

-haemorrhagic risks due to thrombocytopenia, frequent

-metabolic and renal dysfunctions, frequent

Risks related to the transplant procedure (expected mortality < 20%):

-Risks related to the toxicity of the chemotherapy are listed in the investigator brochure. In summary:

-Thiotepa:

-myelosuppression

-gastrointestinal tract: anorexia, nausea, vomiting, stomatitis, mucositis, abdominal pain

-skin: Skin rash and bronzing of the skin, redness, flaking, and peeling

-CNS: headache, confusion, « hallucinations », convulsions, encephalopathy (dose and age dependant : > 500 mg/m^2 and > 60 years)

-Fludarabine:

-myelosuppression, lymphopenia, haemolytic anemia

-fever, chills, infections

-gastrointestinal tract: nausea, vomiting, diarrhea

-CNS: weakness/fatigue, headache, hearing disturbances, paresthesias, confusion, visual disturbances and encephalopathy.

-Busulfan:

-myelosuppression, lymphopenia
-infections
-skin: hyperpigmentation
-hepatic: hepatic veno-occlusive disease
-gastrointestinal tract : nausea, vomiting
-genitourinary: haemorrhagic cystitis
-CNS: seizures, convulsions

-Thymoglobuline:
-lymphopenia, neutropenia, thrombopenia
-fever, chills, anaphylactic reaction
-infections
-EBV induced lymphoproliferative disease

-Morbidity and mortality related to acute and chronic GVHD: expected grade II-IV acute GVHD < 30%, expected chronic GVHD <50%
-Morbidity related to prolonged hospitalisation: asthenia, anorexia, weight loss, nosocomial infections

-Psychological risks:
They are related to the mortality risk of the disease and the morbidity of the transplant procedure

-Socio-economical risks:
Not applicable

-Risks related to the research:
Not applicable

2.7.2.2 Collective risks:
Not applicable

2.8 Balance benefits/risks

The balance is in favour of the benefits. Indeed, the procedure is proposed to patients with a high relapse risk. CBT with RIC has been shown to be able to reduce the relapse risk and the conditioning proposed in this trial should reduce the relapse risk without excess of toxicity.

2.9 Recruitment – eligible patients in the centers

According to the number of CBT performed in the different teams involved in this project in 2010 (Data from the SFGM-TC registry), the expected inclusions for the proposed study for a two year period of recruitment are:

N°	Name	Surname	Town	Country	Expected recruitment/**year**	Total
1	Rubio	Marie-Thérèse	Saint Antoine,	France	5	10

			Paris			
2	Peffault de la Tour	Régis	Saint Louis, Paris	France	7	14
3	NGuyen	Stéphanie	Pitié, Paris	France	1	2
4	Coiteux	Valérie	Lille	France	2	4
5	Milpied	Noel	Pessac	France	2	4
6	Michallet	Mauricette	Lyon	France	3	6
7	Chevallier	Patrice	Nantes	France	5	10
8	Huynh	Anne	Toulouse	France	2	4
9	Deconinck	Eric	Besançon	France	2	4
10	Maillard	Natacha	Poitiers	France	2	4
11	Reman	Oumedaly	Caen	France	2	4
12	Fegueux	Nathalie	Montpellier	France	4 to 8	8 to 16
13	Turlure	Pascal	Limoges	France	1 to 2	2 to 4
14	Cornillon	Jérôme	Saint Etienne	France	1 to 2	2 to 4
15	Charbonnier	Amandine	Amiens	France	1 to 2	2 to 4
16	Lioure	Bruno	Strasbourg	France	2 to 4	4 to 8
17	Contentin	Nathalie	Rouen	France	1 to 2	2 to 4
18	Bulabois	Claude Eric	Grenoble	France	1 to 2	2 to 4
19	Clément	Laurence	Nancy	France	1	2
20	Bay	Jacques Olivier	Clermont Ferrand	France	1 to 2	2 to 4
				Total	**46 to 58**	**92 to 116**

3. STUDY OBJECTIVES

3.1 Main objective

The primary objective is to determine the safety and efficacy of a pre-transplant reduced toxicity conditioning regimen (thiotepa, busulfan, fludarabine and ATG) followed by unrelated cord blood allogeneic stem cell transplant for high risk myeloïd malignancies.

3.2 Secondary objectives

- Incidence of engraftment after transplantation
- Incidence and severity of acute graft-versus-host-disease (GVHD)
- Incidence and severity of chronic GVHD
- Rate of disease relapse at one year after transplantation
- Quality of life
- Ancillary study: immune recovery of peripheral blood lymphocyte subsets (B, NK, T CD4, T CD8, T regs, iNKT, dendritic cells) and analysis of KIR mismatches between patient and cord blood cells

4. ENDPOINTS

4.1 Primary endpoint

Cumulative incidence of NRM at 12 months after transplantation.

4.2 Secondary endpoints

- Incidence of neutrophil engraftment (day and proportion of patients reaching neutrophils $>0.5x10^9/L$); and platelets recovery (day and proportion of patients reaching platelets > 20 x 10^9 / L without transfusion) after transplantation

- Incidence and severity of acute GVHD (diagnosed and graded as standard criteria detailed in Appendix 4)
- Incidence and severity of chronic GVHD (diagnosed and graded as standard criteria detailed in Appendix 4)
- Incidence of disease relapse at one year after transplantation (relapse is defined on the basis of morphologica evidence of leukemic cells in the bone marrow or other sites)
- Disease-free survival at one year after transplantation (time from transplantation to either first relapse or death in complete remission)
- Overall Survival at one year after transplantation (time from transplantation to death from any cause)
- Evaluation of the quality of life (using a french translation of the FACT-BMT (version 4.0) (cf. Appendix 6).
- Immune recovery of lymphocyte subsets at 1, 2, 3, 6 and 12 months post-CBT.30 ml of peripheral blood per point will be sent to the investigator's central collection laboratory for secondary analysis of B, NK, T CD4, T CD8, T regs, iNKT, dendritic cells recovery (cf. Appendix 7).
-Analysis of KIR mismatches between patient and cord blood units (cf. Appendix 7).

7.

5. STUDY POPULATION

5.1 Inclusion criteria

1) Age ≥18 years and ≤ 65 years
2) Patients diagnosed with one of the following diseases:
   - Acute myelogenous leukemia (AML) beyond CR1 or in CR1 with high risk features (≥ intermediate risk 2) (cf. appendix 2)
   - Myelodysplastic syndromes with International Prognostic Scoring System (IPSS) score ≥ 2 (cf. appendix 3)
3) Absence of a matched sibling or unrelated donor (10/10 or 9/10 if mismatch on HLA Cw, based on each center's donor selection criteria)
4) Cord blood units must be matched with patient at 4, 5, or 6/6 HLA loci, (class I antigenic & class II allelic level)with a minimum of 4 x 107 TNC/kg recipient body weight in the pre-thawed fraction and with ≥2.5x107 TNC/kg per cord blood unit in case of 2 cord blood units
5) Performance status : OMS score ≤ 1 (cf. appendix 5)
6) Cardiac function - left ventricular ejection fraction ≥ 45%.
7) Pulmonary function - diffusion capacity of at least 50% predicted.
8) Serum creatinine clearance ≥ 50 ml/min.
9) SGPT ≤ 4x normal , serum bilirubin < 2 x normal.
10) Written informed consent.
11) Progestative treatment for women with persisting menstrual periods

5.2 Exclusion criteria

1) Presence of a matched sibling or unrelated available donor (10/10 or 9/10 if mismatch on HLA Cw in centers performing 9/10 HLA mismatched transplants)

2) Active infection at time of conditioning. In case of uncertainty regarding whether a previous infection is resolved or not, this will be discussed with the PI on a case by case basis.
3) Pregnancy in women with child bearing potential (pregnancy test performed within 2-4 weeks of study entry).
4) HIV positive
5) Active CNS leukemia
6) Chronic or active Hepatitis B or Hepatitis C. If questions about liver health discuss with PI and strongly consider liver biopsy.
7) Poor performance status : OMS score > 1 (cf. appendix 5)
8) Life expectancy is severely limited by concomitant illness and expected to be <12 weeks.
9) Left ventricular ejection fraction <45%. Uncontrolled arrhythmias or symptomatic cardiac disease.
10) Symptomatic pulmonary disease. FEV1, FVC and DLCO <50% of expected corrected for hemoglobin.
11) Serum creatinine clearance (Crockoft) below 50 mL/m per 1.73 m² or requiring dialysis
12) Vaccination with alive vaccine (virus or bacteria) < 3 months
13) Fludarabine contra-indication
14) Thymoglobuline contra-indication
15) Patient under guardianship or curatorship

6. INVESTIGATIONAL PLAN

6.1 Overall study design

This is a prospective, multicenter (n= 20), non-randomized Phase II (one step A'Hern procedure) study.

8. 6.1.1. Pre-transplant assessment

Information on the expected benefit of an allogeneic HSCT to treat his haematological disease will be first given to the patient as soon as the indication of the transplant has been set-up. The need for an alternative graft in the absence of a sibling or unrelated matched donor will be exposed at the same time to optimize the time of research.

Once the indication of allogeneic HSCT is raised, an HLA typing of the patient will be performed. If the patient does not have any suitable sibling or unrelated donor identified and available in the two months following the complete remission, the research for two suitable cord blood units will be initiated.

After achieving the complete pre-transplant chemotherapy schedule, a pre-transplant assessment will be performed in the 4 weeks before the scheduled transplant day in order to check the eligibility criteria.

Cases of patients with co-morbidities or above 60 years old should be submitted to advice of the principal investigators before inclusion in order to validate their eligibility to the study.
During the month before the transplant and prior to entry into the trial, the participating investigators (or designated assistant) will expose the nature of the trial, its purpose, procedures, expected duration, alternative therapy and the benefits and risks of CBT with reduced intensity/toxicity conditioning. Each patient will be given the opportunity to ask questions and will be informed of the right of the patient to withdraw from the trial at any time without prejudice. Consent forms will be signed during the pre-transplantation validation consultation.

9. 6.1.2. Patients selection and registration

Patients are included if:
- they fulfil the inclusion and exclusion criteria defining eligibility for "reduced-intensity/toxicity conditioning" regimen
AND
- an evaluation for organ functions has not revealed any exclusion criteria as defined,
AND
- 1 or 2 suitable unrelated cord blood units have been identified
Inclusion will be registered in the e-CRF by investigators in real time.

10. 6.1.3. Cord blood unit selection

Identification of one or two cord blood units matched with patient at 4, 5, or 6/6 HLA antigens with a min. total of 4 x 10^7 TNC/kg recipient body weight in the pre-thawed fraction and a minimum of 2.5x10^7 TNC/kg per cord blood unit in case of 2 cord blood units.

Cord blood selection is performed on the basis of a serological determination of HLA-A and B and molecular for digit resolution for HLA DRB1. The final selection of the most suitable cord bloods is at the discretion of the transplant physician.
Grafts are transfused without any further manipulation such as T-cell depletion and $CD34^+$ selection are not permitted. Transplantation should be performed within 4 hours from thawing.

11. 6.1.4. Treatment plan

Cord blood transplant will be performed on Day 0, 7 days after the beginning of the conditioning regimen that will include:

Conditioning regimen	Nb inj /d	Way	Solvant	Volume of dilution	Duration	D-7	D-6	D-5	D-4	D-3	D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7
Thiotepa 5mg/kg/day	1	IV	SG5%	250 ml	1H	**x**	**x**													
Fludarabine 40 mg/m^2/ day	1	IV	NaCl 9%	250 ml	1H			**x**	**x**	**x**	**x**									
Busilvex 3.2 mg/kg/day	1	IV	NaCl 9%	250 ml	3H			**x**	**x**	**x**										
Thymoglobuline 2.5 mg/kg/day	1	IV	NaCl 9%	500 ml	8h					**x**	**x**									
CBT													**x**							
Associated treatements																				
Rivotril 0.03 mg/kg/day	1	IV	SG5%	PSE	24H		●	●	●	●	●									
CSA 3 mg/kg/day	1	IV	SG5%	PSE	24H					○	○	○	○	○	○	○	○	○	○	○
MMF30 mg/kg/day in 2 injections/day	2	IV	SG5%	100 ml	30min					●	●	●	●	●	●	●	●	●	●	●
GCSF 5µg/kg/day *	1	SC																		►
** until PNN>4x10^9/L for > 3 days																				

6.2 Study duration

Study duration: 36 months

Recruitment: 24 months

Duration per patient: 12 to 36 months, depending on the time on enrollment.

6.3 Randomisation

Not applicable

6.4 Blinding

Not applicable

7. SCHEDULE OF ASSESSEMENT

7.1 Evaluation before inclusion into the study in the 15 days before inclusion

Function of organ systems have to be documented before inclusion, as outlined in the inclusion criteria. This includes physical exam, chest x-ray, ECG, echocardiogram, lung function test, liver function tests, serum creatinin, BUN, total protein, pregnancy test and usual pre-transplant serologies (HIV1 and 2, p24 HIV Ag, HTLV1 and 2, HBV, HCV, CMV, EBV, toxoplasmosis, TPHA-VDRL).

Disease status should be evaluated with blood cell counts including a differential count of white blood cells, a bone marrow aspiration. In addition, immunophenotyping of blast cells should be performed in the presence of a specific marker at diagnosis as well as the evaluation of the residual molecular disease in the presence of a quantitative molecular marker.

Charts of patients with co-morbidities (history of fungal infection or presenting an organ dysfunction) or above 60 years old should be submitted to the advice of the principal investigators for a central validation of the eligibility criteria.

7.2 Evaluation before start of conditioning in the 15 days before starting conditioning

A routine exam of clinical chemistry values is performed according to local standards. For examination of chimerism, samples from patient and donor have to be collected and stored.
Quality of life is assessed (cf appendix 6) before starting the conditioning.
A first blood sample of 20 ml from the patient will be sent to the investigator's central collection laboratory.

7.3 Evaluation of early post-transplant evolution (from day 0 to Day 100)

- day of neutrophil (>500/µl) and platelets (first of three days with >20G/l without transfusion) engraftment
- performance status
- maximum toxicity with respect to mucositis, liver, kidney, lung, heart, neurological system according to CTC criteria (cf. appendix 8)
- infections (bacteremia, fungemia, invasive fungal infection, CMV reactivation and disease, other viral reactivation or infection),
- acute GVHD (cf. appendix 4)
- Bone marrow aspiration with evaluation of morphological response and residual disease by phenotyping and molecular analyses (whenever appropriate) as well as chimerism from peripheral blood (cf. appendix 9)
- Checking that blood samples of 40 ml for immune reconstitution studies have been drawn at 1 and 2 months and sent to the investigator's central collection laboratory (cf Appendix 7)

7.4 Evaluation during follow up after day 100

At day 100, 6, 12 months from allo-SCT and at the end of study :

- Performance status
- maximum toxicity with respect to mucositis, liver, kidney, lung, heart, neurological system according to CTC criteria (cf. appendix 8)
- blood counts
- infections (bacteremia, fungemia, invasive fungal infection, CMV reactivation and disease, other viral reactivation or infection)
- grade of acute or chronic GVHD (cf. appendix 4)
- date of discontinuation of immunosuppressive medication (if appropriate)
- at day 100 and 12 months: bone marrow aspiration with evaluation of morphological response and residual disease by phenotyping and/or molecular analyses (whenever appropriate) as well as chimerism from peripheral blood (cf. appendix 9). To be repeated whenever necessary in case of suspicion of relapse.
- quality of life assessment (cf appendix 6)
- Checking that blood samples of 40 ml for immune reconstitution studies have been drawn at day 100, 6 and 12 months post-transplant and sent to the investigator's central collection laboratory (cf appendix 7)
- At the end of the study: checking the aliquots of cord blood units have been sent from the cell therapy department to the investigator's central collection laboratory (cf appendix 7)

Study chart :

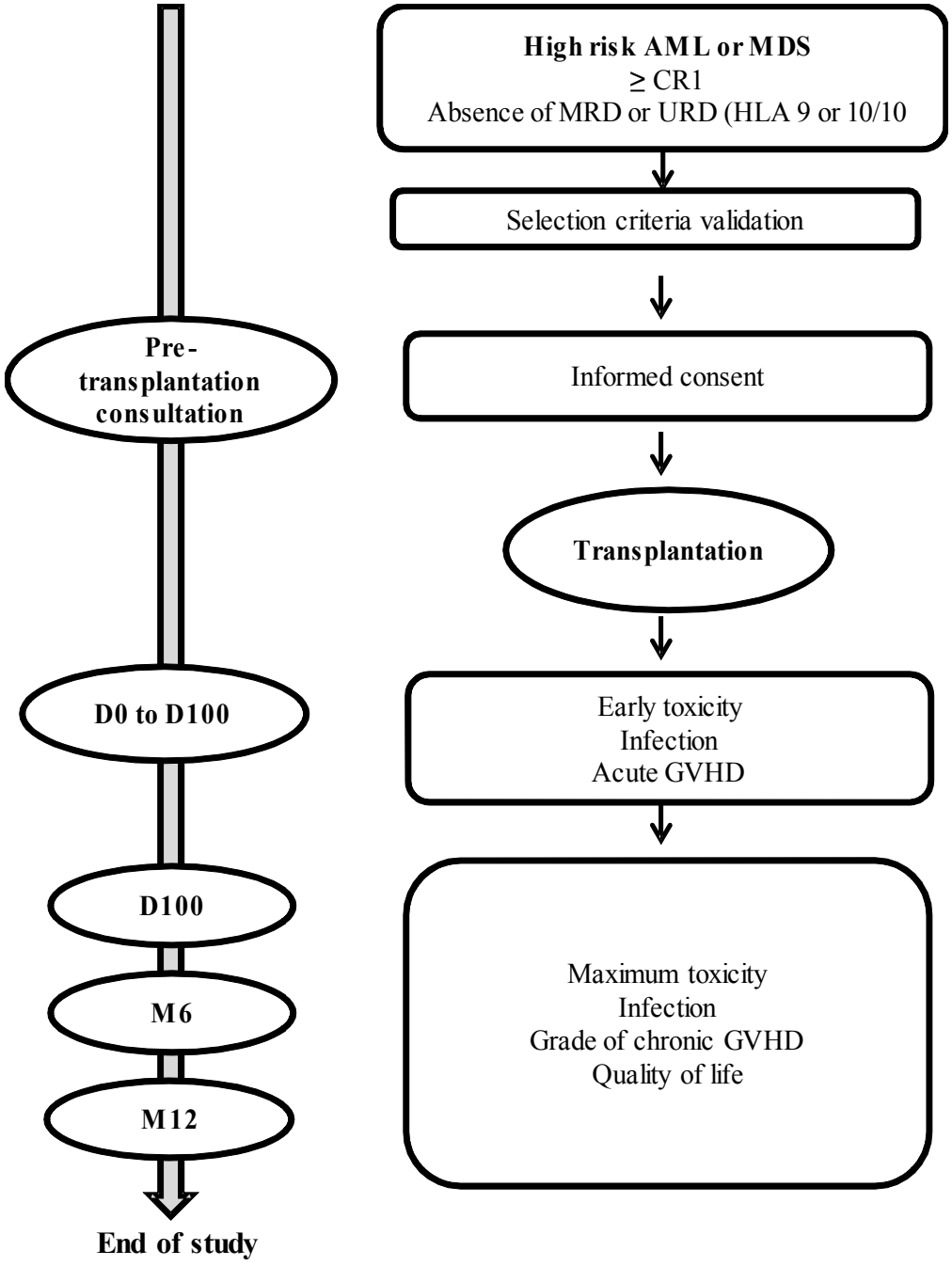
	<15 days before inclusion	Inclusion	Conditionning D-7 tà D-2	D 0	D30	D60	D100	6 months	12 months	End of study
identified CBU	x									
Informed consent	x	signature								
Medical history	x									
Physical exam (P. Status, infections)	x				x		x	x	x	x
Pregnancy test	x									
Viral Serologies	x									
WBC, liver and renal functions	x				x		x	x	x	x
Chest X-ray, lung function tests	x						x	x	x	x
ECG and echocardiogram	x								x	
Inclusion criteria validation		x								
Inclusion fax		x								
Disease evaluation (marrow aspiration +/- phenotyping +/- residual molecular disease)	x						x		x	
Fax for beginning conditioning			x							
CBT				x						
Chimerism	x				x		x		x	
Immune reconstitution	R				R	R	R	R	R	
Quality of life assessment		R			R		R	R	R	R
Send CB frozen aliquots *				R						R

Legend : R = Research / X= Care

CBU: cord blood unit, P. status: performans status, ECG : electrocardiogram, Disease evaluation: WBC counts + bone marrow aspiration +/- immunophenotyping +/- molecular biology (MRD).

*: one aliquot from each CBU kept in the cellular therapy departments involved in the study will be sent to the investigator's central collection laboratory at the end of the study for analyses of KIR mismatches.

Flow chart



7.5 Biobank

Blood samples (40 ml per time point) collected at day 30, day 60, day 100, 6 and 12 months post-tranplant will be sent within 24 hours to the investigator's central collection laboratory : URC des Hôpitaux Universitaires de l'Est Parisien (URC-Est) at Saint-Antoine Hospital, Paris. Peripheral blood mononuclear cells (PBMC) will be isolated from 30 ml of blood by density-gradient

centrifugation. PBMC will be frozen in vials of the concentration of 5 to 10 x 10^6 cells/ml, labelled and stored for 15 years at -180°C in the central collection laboratory of Saint Antoine hospital.
Those samples will be used to perform ancillary studies of immune reconstitution.

At the end of the study, one aliquot of each cord blood unit kept in the corresponding cell therapy departments will be sent to the investigator's central collection laboratory : URC des Hôpitaux Universitaires de l'Est Parisien (URC-Est) at Saint-Antoine Hospital, Paris.
Those samples will be used to analyse KIR mismatches between CBU and recipients.

8. TREATMENTS

8.1 Description of the investigational products

The conditioning regimen will include:
- IV Thiotepa (5 mg/Kg/day for 2 days) (Day -7 and -6)
- IV fludarabine (40 mg/m²/day for 4 days) (from Day-5 to day -2)
- IV Busulfan (Busilvex 3.2 mg/kg/day for 3 days) (Day-5, -4 and -3)
- IV Anti-thymocyte globuline (Thymogobuline®, 2.5 mg/kg/day for 2 days) (Day-3 and -2)

➔Administration regimen:

- Thiotepa (Thiotepa specific for each pharmacy) :
    * 5 mg/Kg/day in 250 ml of Glucose 5% serum administered in 1 hour by intravenous injection
    * for 2 days, on days -7 and -6

- Fludarabine (specific for each pharmacy) :
    * 40 mg/m2/day in 250 ml of NaCl 0.9% physiological serum administered in 1 hour by intravenous injection (hospital centralized pharmacy preparation)
    * for 4 days, from Day -5 to -2

- Busulfan (Busilvex® or another brand name):
    * 3.2 mg/kg/day for 3 days, i.e. 9.6 mg/kg total dose in 250 ml of NaCl 0.9% physiological serum administered in 3 hours by intravenous injection
    * With prophylactic anti-comitial treatment (for instance, Valium® morning and evening on the day before administration of Busulfan or 24H IV Rivotril 0.03 mg/kg/day started at least 2 hours before the administration of Busulfan, then until the day following (inclusive) the final day of administration of Busulfan)
    * From Day -5 to day -3

- Anti-thymocyte Globulin (Thymoglobuline® or another brand name)
    * 2.5 mg/Kg/day in 500 ml of NaCl 0.9% physiological serum administered by intravenous infusion for at least eight hours

*Premedication using corticosteroids and antihistamines (depending on the routine practice in each participating centre)
*for 2 days on Day-3 and Day-2

8.2 Investigational drug management

The TBF -Cord study is an institutional is a trial sponsored by APHP non profit organization. These experimental drugs are used in the indication of their marketing authorization. So their providing complies with the French article L1121 -16- 1 of the Code of Public Health which allows the investigational medicinal product to be covered by the national health insurance funds.

They will be provided by the hospital pharmacies and thus, they will not be specifically provided by the sponsor.

All specialties and available presentations can be used.

At the beginning of the trial, the sponsor will check that the study drugs are available in each participating center in the study and that all hospital pharmacies agree to participate (preparation, storage,labelling…).
Accordance with the rules of good Practices and to track the treatment given to each patient, all the information related to the treatment (batch traceability, compliance ...) will be collected.

Labels for traceability of experimental medicines will be provided to the hospital pharmacies by the sponsor. (Annexe 11 – circuit pharmaceutique)

8.3 Concomitant therapies

➔ **GVHD prophylaxis:**

- Cyclosporine A (CSA): 3 mg/Kg/ day from day-3 in continuous infusion, to be changed to oral dosing whenever tolerated. Residual serum levels 12 hours after the last oral administration should be comprised between 200 and 300 ng/ml.
- and Mycophenolate Mofetil (MMF): 30 mg/kg/day in IV injections or 4 oral doses, from day-3

As a general guideline, MMF and CSA can be tapered after transplant starting from day 30 for MMF and 90 for CsA, if no GVHD is present.

➔ **Graft infusion at day 0** and premedication according to local practice

➔ **GCSF from day +7** at the dose of 5 µg/kg/day until granulocyte recovery (WBC > 4.10^9/L for 3 consecutive days).

➔ **Supportive care:** will be performed according to each participating centre usual practice. As in standard transplant protocols, patients are monitored daily from the day of transplantation until the

last day of hospitalization. Subsequently, the monitoring frequency will be adapted according to standard criteria.

➔ **Other treatments administration**

Treatment administration for Fludarabine, Thiothepa, Thymoglobuline, and IV Busulfan should be done according to the protocol. All other concomitant medications shall follow standard transplant procedures as per local procedures (e.g. Antiemetics) should be administered per institutional guidelines prior to the first dose of Bu and continued on a fixed schedule through 12-24 hours after the last dose of Bu.

➔ **IF NOT MANDATORY OR NECESSARY**, THE USE OF PARACETAMOL SHOULD BE AVOIDED 72 HOURS BEFORE AND DURING BUSULFAN ADMINISTRATION, SINCE IT INTERFERES WITH THE METABOLISM OF BUSULFAN AND MAY CONTRIBUTE TO SERIOUS LIVER DAMAGE.

➔ **Other drugs** known to interfere with the metabolism of busulfan should not to be concomitantly used during the chemotherapy administration up to and including the day of transplantation. In particular, voriconazole, itraconazole, and metronidazole as well as Tyrosine-kinase inhibitor therapy must be omitted for at least 10 days prior to admission for transplantation on this program since these agents have well described interference with busulfan. They can be resumed on or after the day of the stem cell transplant as indicated for the individual patient.

A noter :

Associations non recommandées :

Thymoglobuline® avec :

- *vaccin vivant atténué : risque d'infection générale voire fatale*

Fludara® avec :

- *pentostatine : risque d'accident pulmonaire mortel*
- *dipyridamole ou autre inhibiteur du captage de l'adénosine : risque de diminuer l'efficacité thérapeutique de Fludara®*

Thiotepa avec :

- *Phénytoïne : risque de survenue de convulsions*
- *Fosphénytoïne : risque de survenue de convulsions*
- *vaccin vivant atténué : risque de maladie vaccinale généralisée voire mortelle*

Associations contre-indiquées :

Avec le conditionnement test, il est contre indiqué l'utilisation concomitante des vaccins vivants atténués (fièvre jaune, etc..) et des vaccins bactériens.

9. PREMATURE DISCONTINUATION

9.1 Subject discontinuation

A premature discontinuation is defined when a patient selected in a trial ceases its participation before the end of study.

The criteria for premature discontinuation of the study are:

- Patient's refusal to continue the study
- Cancellation of allo-SCT
- Lost for follow up: In such a case, the investigators must make every effort to contact subjects lost to follow-up.

In case of premature discontinuation during the selection period, the patient will be replaced and his data will not be taken into account for analysis. However, monitoring of patients who have undergone allo-SCT will be pursued, even if they have ceased their participation in the trial. In addition, monitoring of patients who are included in the protocol, but who ceased their participation in the trial, will be pursued.

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded when the subject signed the consent form.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

The case report form must list the various reasons for ending participation in the research:

- ☐ Ineffective
- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent

9.2 Study discontinuation

Premature termination of the clinical trial may be decided by the promoter and/or Health authority and/or the scientific comityat any time.

Premature discontinuation of the study shall also occur in case there is:

1 – Delay or absence of neutrophil recovery (ANC <500 at day+60) in at least 25% of patients, in the absence of ongoing GVHD or antiviral treatment against cytomegalovirus or disease progression. These criteria will be studied at day 60 after inclusion of the first 10 patients. The stopping rules for the absence of neutrophil recovery ≥25% are as follow:

≥3/10 patients (lower limit of the 90% confidence interval).

2 – Excessive transplant-related mortality at day 100 after allo-SCT ≥ 25%

This criterion will be studied at day 100 after inclusion of the first 10 patients. The stopping rules for a rate of transplant related mortality ≥25% are as follow:

≥3/10 patients (lower limit of the 90% confidence interval).

10. SAFETY ASSESSMENT – RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Procedures in place for recording and reporting adverse events

10.1.1 Definitions

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012) :

Adverse event Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**
  Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction**
  An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product.

According to the notice to sponsors of clinical trials for medications (ANSM):

- **New safety issue**

Any new information regarding safety:
- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction occurring

b) suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial
- a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness
- significant safety results from a recently completed research carried out on animals (such as a carcinogenicity research)
- the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons
- an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out 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 trial carried out in a different country but relating to the same medication

D'après l'article R. 1211-31 du Code de la Santé Publique, on entend par :

- ***Incident** : une défaillance ou altération d'un élément isolé, d'un processus ou d'un système, liée aux activités mentionnées au 1° de l'article R. 1211-30 [prélèvement, collecte, fabrication, préparation, transformation, conservation, transport, distribution, cession, importation, exportation, répartition, attribution, greffe ou administration], dû à un accident ou à une erreur, et susceptible d'entraîner un effet indésirable chez le patient, le donneur vivant ou le receveur ;*

- ***Incident grave** : un incident susceptible de se répéter et pouvant mettre en jeu la sécurité d'un ou plusieurs patients, donneurs vivants ou receveurs, et tout incident pouvant entraîner un effet indésirable grave.*

10.2 Reporting Procedures for All Adverse Events

10.2.1 The investigator's role

Adverse events that do not require immediate reporting are recorded on the case report "adverse events" form.

10.2.2 The sponsor's role

This concerns all new safety issue that might significantly modify the evaluation of the benefits/risks ratio of an investigational medicinal product or the research, or that might lead to envisaging modifications concerning the investigational medicinal product administration or in the overall conduct of the trial.

10.3 Serious adverse event reporting procedures

10.3.1 The investigator's role

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events:
- either by using an adverse events rating scale, attached to the protocol
  - Common Terminology Criteria for Averse Events (v4.0) [National Cancer Institute]
  - Glucksberg Thomas Scale for any graft versus host reactions
  - GREFIG Score for any infections

The investigator assesses the causal relationship between the serious adverse events and the experimental medication(s), the procedures added by the research (blood cord transplantation)

12. Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

- ***<u>Serious adverse events that do not require the investigator to immediately notify the sponsor</u>***

These serious adverse events are only recorded in the "adverse event" section of the case report form.

- **<u>Normal and natural evolution of the pathology</u>:**
  - hospitalization planned for the follow-up of the studied condition(myeloid malignancies)
  - hospitalization for standard care or monitoring of the studied condition non associated with degradation of patient state.

- **<u>Special circumstances</u>**

  - hospitalization for preexisting condition
  - hospitalization for medical treatment or surgery planned before the inclusion.
  - Hospital admission for social reasons or administrative reason
  - Aplasia induced by the conditioning therapy from day 0 until engraftment

- **<u>Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research</u>**

  Related to other concomitant treatments (e.g. growth factors, analgesic drugs, anti-emetic drugs, immunosuppressive therapy) : the investigator must declare to the competent authorities according to the spontaneous notification.

➢ ***<u>Serious adverse events that require the investigator to immediately notify the sponsor</u>***

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 10.3.3.1 as not requiring notification: 1- Death 2- Life threatening situation 3- Requiring hospitalisation or prolonging hospitalisation 4- Persistent or significant disability or incapacity 5- Congenital abnormality or birth defect 6- Or any other adverse event considered "medically significant"

❖ For serious adverse events related to the experimental medication(s) and which are expected:
Refer to SmPC of fludarabine, Thiotepa, Thymoglobuline, busulfan

- The most frequent events related to study products (fludarabine/Busulfan/Thymoglobuline) are :
  - Related to immunosupression such as infectious complications (candidosis, herpes-zoster, pneumonia, bacteremia, septicemia, septic choc…)
  - Related to transient hematological toxicity (anemia, leuco-neutropenia with or without fever, thrombocytopenia, aplasia…)
  - Related to toxicity on the mucosal and cutaneous tissues: mucositis, rash, dermatitis ,alopecia…
  - Related to digestive toxicity (nausea, vomiting, anorexia...)

- related to fertility and teratogenicity concerns:

<u>Busulfan</u> : Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Busulfan has caused embryofoetal lethality and malformations in pre-clinical studies. There are no adequate data from the use of either busulfan in pregnant woman. A few cases of congenital abnormalities have been reported with low-dose oral busulfan, not necessarily attributable to the active substance, and third trimester exposure may be associated with impaired intrauterine growth.Women of childbearing potential have to use effective contraception during and up to 6 months after treatment.

Busulfan can impair fertility in male too. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. Therefore, men treated with Busilvex are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Busilvex.

❖ The serious adverse events related to blood cord transplantation are listed in the Investigator's Brochure. The most frequent adverse reactions are :
  - Graft Versus Host reaction (GVH), grade ≥ 3 (Glucksberg Thomas scale)
  - Infections grade 3 (GREFIG scale)

❖ For serious adverse events related to GVH prophylactic medication and which are expected :
Refer to SmPC of Neoral® (ciclosporine) and Cellcept® (mycophénolate de mofetil)

- ***In utero* exposure**

The sponsor must be notified immediately about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.

Notification is required if the exposure involves:
- the mother,
- the father if the experimental medication is genotoxic.

- **Exposure while breastfeeding**

Exposure while breastfeeding occurs if an infant or child could have been exposed to a medication *via* the breast milk of a mother being treated with an experimental medication.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor about exposure while breastfeeding as soon as the investigator becomes aware.

10.1.1 Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see Appendix 10). The report must be signed by the investigator.

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

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.

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

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division of the DRCD, fax No. **01 44 84 17 99**.

For studies using e-CRF:
- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in Appendix 10**.** As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCD can be contacted via email: vigilance.drcd@drc.aphp.fr

***In utero* exposure**
The investigator must notified immediately the sponsor any pregnancy during which the foetus (from the pre-embryonic stage up to birth) and exposure during breast feeding could have been exposed at a given time to an experimental medication, even if the pregnancy or the breast feeding is not associated with an adverse event.

The investigator completes the "form for monitoring a pregnancy that developed during a biomedical research", found in Appendix and sends it by fax to the Vigilance Division at **01 44 84 17 99**.

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 SAE.
If the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

The initial pregnancy notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division - of the DRCD, fax No. **01 44 84 17 99**.

10.3.2 Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects:

- after the date on which the consent was signed
- throughout the period during which the participant is monitored, as determined by the research
- with no time limit, if the SAE is likely to be due to the experimental medication or to the research procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.3.3 The sponsor's role

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.

- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Le promoteur déclare les incidents graves dans un délai de 15 jours après la prise de connaissance. Les informations complémentaires pertinentes sont transmises dans un nouveau délai de huit jours à compter du délai de quinze jours (article R1123-47).

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSAR.

10.3.3.2 Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

10.3.3.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

10.3.4 Biovigilance procedures reporting

Obligation of health professionals (investigator, local correspondent for biovigilance, responsable for cell therapy unit)

Any health professional who has knowledge of an incident or an adverse event occurring in the donor shall notify the sponsor within 48 hours. It could be the local correspondent for biovigilance, investigator, producer, or head of Unit Cell Therapy. The health professional fills the biovigilance form and send it by fax to the Clinical Research Unit at 01 49 28 28 13. – annexe 12

As a reminder, regarding the incidents of the process of transplantation, biovigilance is not intended to receive all non-conformities already managed by the good manufacturing practice of an institution (health facility, Unit Cell Therapy). Only incidents occurring a finished product and validated will be reported, or a non-validated product when it could be a **loss of opportunity for the patient** (eg loss of product or risk getting a finished lower quality product in reference of specifications).

In all cases, it is not necessary to have all the expected part of the investigation for the occurrence or the adverse event elements to alert the sponsor (AP-HP). The additional information will be sent secondarily as needed.

Any relevant documents (hospital report, Form batch release, results of chimerism ...) should be sent to the sponsor to the extent possible.

11. STATISTICS

11.1 Calculation of the number of patients

Based on results from the literature, the hypothesis for the primary endpoint is an improvement in non-relapse mortality at one year after transplantation from 35% to 20%. Using a one-step A'Hern procedure, 55 patients are needed. In all, 57 patients will be included (taking into account that after registration, there is a risk of dropout i.e. a patient who will not receive a transplant due to rapidly progressive disease, infection or other events occurring after planning the transplant, but before start of conditioning). If the number of patients dying of NRM at one year is 13 or less, the hypothesis that NRM $\geq$ 0.35 is rejected with a target error rate of 0.050 and an actual error rate of 0.049. If the number of patients dying of NRM at one year is 13 or less, the hypothesis that NRM $\leq$ 0.20 is rejected with a target error rate of 0.20 and an actual error rate of 0.197.

11.2 Dealing with missing data

Every effort will be made to keep the number of missing values for all parameters to a minimum. Missing data on overall survival is assumed to be 0 and on event free survival to be below 10 % as patient care after transplantation is very close.

11.3 Statistical analyses

Every patient included in the study and who was actually transplanted, will be taken into account at time of data analysis. A descriptive analysis will be conducted on the following parameters:

- The characteristics of donors and patients
- Primary and secondary endpoints

Qualitative data will be described in frequency and percentage and will be represented using histograms or diagrams of distribution. They will be compared using the X2 test or Fisher exact test. Quantitative data will be described using the calculations of average, standard deviation, median, and extreme values, and will be compared with the Mann & Whitney nonparametric test.
The toxicities rate will be calculated and will be given with their 95% confidence intervals.
The probabilities of survival will be estimated by the Kaplan-Meier method and by calculating the cumulative incidences for relapse/progression, GVHD and NRM incidence.
All tests will be bilateral, and the level of significance is 0.05.

12. STUDY COMMITTEE

12.1 Executive committee

It will be constituted by main clinical investigators of the trial, the biostatistician, representatives of the sponsor and of the URC. It will define the general organization and practical functioning of the trial, and will coordinate information received. It will determine trial methodology, will closely monitor the trial especially with regard to safety and may propose trial amendments in case of unexpected events.

12.2 Data Safety Monitoring Committee

The Data and Safety Monitoring Board (DSMB) can 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 members of the DSMB will be named after the research starts. During the first meeting of the DSMB, a chairman will be appointed and the members will determine their operating methods and the meeting schedule.
All missions as well as the precise operating methods of the DSMB will be described in the DSMB's charter for the research.

<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 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:

- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting.

The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and the CPP.

The DSMB will assess at regular intervals the progress of the trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop the trial.

During the study, meetings of the DSMB will be organised periodically (i.e. on inclusion of five, 10, 15 patients etc.).

At the request of ANSM, the DSMB will meet for the evaluation of the first 10 included patients.

The members of this committee are listed below: (modifications in progress)

Name	Speciality	Address	E-mail
Felipe Suarez	Clinical haematology	Necker hospital	felipe.suarez@nck.aphp.fr
Sébastien Maury	Clinical haematology	Mondor hospital	sebastien.maury@hmn.aphp.fr
Marina Cavazzana-Calvo	Cell Therapy	Necker hospital	m.cavazzana@nck.aphp.fr or marina.cavazzana-calvo@fondationimagine.org
François Lemoine	Cell Therapy	Pitié Salpétrière hospital	francois.lemoine@psl.aphp.fr

All reports of meeting of the DSMB will be transmitted to the competent authority and ethics committee.

13. DATA HANDLING AND QUALITY ASSURANCE

13.1 Case report form handling

Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-EST.
Data will be entered by the investigator with the help of a Clinical Research Technician (CRT) of URC-Est for AP-HP centers and of each center for others centers.

All information required according to 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. Each missing data item must be coded.
This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
When the investigators complete the case report 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. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.2 Quality control and Assurance

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP.

13.2.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.

The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

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

13.2.2 Strategy for opening the centres

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan.

13.2.3 Level of centre monitoring

In the case of this research, which is considered C risk, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level elevated.

13.2.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCD's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCD for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

13.2.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.
An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

13.2.6 Primary investigator's commitment to assume responsibility

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

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.3 Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices

- the ANSM authorisations and CPP favourable opinions
- letters of correspondence
- the inclusion list or register
- the appendices specific to the research
- the final research report
    - The data collection documents

13.4 Ownership of the data

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

14. ETHICAL AND REGULATORY ASPECTS

14.1 Responsibilities of Investigators

The investigator will be responsible for insuring that the clinical study is performed in accordance with the protocol, the ethical principle that have their origin in the Declaration of Helsinki as well as the Good Clinical Practice. To do this, a copy of the scientific commitment (standard DRCD document) signed and dated by each investigator given to the representative of the promoter.

14.2 Subject information and consent

In conformance with article L1122-1-1 of the Public Health Code, biomedical research cannot be conducted on a person without his/her free and informed consent, obtained after he/she has been provided with the information mentioned in article L. 1122-1 of the same Code Informing trial subjects.
In application of the provisions of article L 1122-1 of the Public Health Code, a trial subject receives first oral and written information on the biomedical research that enables him/her to give free and informed consent. He/she is informed in a complete and honest manner and in comprehensible terms, of the objectives, risks and constraints of the research, the required monitoring and safety measures, the processing of his/her personal data required for the research, his/her registration in a national trial subject database, his/her right to refuse to participate in the research or the possibility to withdraw his/her consent at any moment, etc. All this information should appear in a written document.
The subject is allowed a reflection period between the time when he/she is informed and the time when he/she signs the consent form.
Consent is given in writing. If it is not possible for the person solicited to consent in writing, the consent is certified by a third party. This third party must have no connection with the investigator or the sponsor.

Free, informed written consent by the subject is obtained of the investigator or by a physician on his behalf before the inclusion of the subject in the research.
The information form and a copy of the consent form, dated and signed by the trial subject, as well as the investigator or the representing physician are given to the subject prior to his/her participation in the research. The investigator keeps the original.
In addition, in the subject's medical record, the investigator shall specify the subject's participation in the research, the methods of obtaining his/her consent as well as the methods of providing information in view of obtaining it.
The investigator keeps the subject's original dated and signed consent form.
At the end of the study, a copy of the information form and the consent form shall be placed in a sealed tamperproof envelope with all of the consent forms. This shall be archived by the sponsor.
The information form and the consent form shall be reviewed notably in case of substantial modification of the research or the occurrence of adverse reactions, under circumstances and conditions provided for by the law (articles L .1123-9 and L. 1123-10 of the Public Health Code).

14.3 Legal obligations

14.3.1 The sponsors role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Development Department (DRCD) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

14.3.2 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.3.3 Request for authorisation to ANSM

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

14.3.4 Commitment to compliance with the MR 001 “Méthodologie de Référence”

AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

14.3.5 Request for the opinion of the CCTIRS (advisory committee on the processing of research information in the area of health) and request for authorisation from CNIL (French data protection authorities)

As the processing of personal data for this research does not fall under the scope of the MR 001 méthodologie de reference, the sponsor must obtain the opinion of the CCTIRS and the authorisation of the CNIL.

14.3.6 Ownership of the data

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

14.4 Modifications 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, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

14.5 Clinical trial insurance and compensation to subjects

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

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

14.6 Final research report and Publication policy

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority’s reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

This publication will include the sponsor's name and the name of the funder.
"The sponsor was Assistance Publique – Hôpitaux de Paris (Département de la Recherche Clinique et du Développement)"
"The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2013 (Ministère de la Santé)"

Publication of the results is realized independently from the outcome of the trial. The study or parts of the study should be published by the writing committee only which consists of the persons in charge of the study as mentioned on the front page (Dr Rubio, Dr Labopin, Pr Simon). According to the EBMT rules, co-authors will be offered to the local PI of participating centres, the order depending on the number of patients included by the respective centres, or depending on their contribution to the protocol or the realisation of the study. Other investigators will be mentioned in the addendum. All publications and/or communications related to this trial should at least mention the central coordinator and the PI of the trial and the sponsor. Urcest will be mentioned in Acknowledgements for its help in logistics and data management.

This research is registered on the website http://clinicaltrials.gov/

15. FINANCING AND INSURANCE

15.1 Funding source

The study was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC 2013.

15.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

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

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17. APPENDIX

17.1 Appendix 1: List of clinical hematology co- investigators

Center N°	Name	Firstname	Town	Country	Hospital	E-mail	Tel	Speciality
1	Rubio	Marie Thérèse	Paris	France	Saint Antoine	marie-therese.rubio@sat.aphp.fr	0149282621	Hematology
2	Peffault de la Tour	Régis	Paris	France	Saint Louis	regis.peffaultdelatour@sls.aphp.fr	0142494121	Hematology
3	NGuyen	Stéphanie	Paris	France	Pitié Salpétrière	stephanie.nguyen-quoc@psl.aphp.fr	0142162823	Hematology
4	Coiteux	Valérie	Lille	France	CHU Lille	valerie.coiteux@chru-lille.fr	0320445551	Hematology
5	Milpied	Noel	Pessac	France	CHU Bordeaux	noel.milpied@chu-bordeaux.fr	0557656511	Hematology
6	Michallet	Mauricette	Lyon	France	CHLS	mauricette.michallet@chu-lyon.fr	0478862233	Hematology
7	Chevallier	Patrice	Nantes	France	CHU Nantes	patrice.chevallier@chu-nantes.fr	0240083994	Hematology
8	Huynh	Anne	Toulouse	France	CHU Toulouse	huynh.a@chu-toulouse.fr	0561779041	Hematology
9	Deconinck Larosa Berceanu	Eric Fabrice Ana	Besançon	France	CHU Besançon	eric.deconinck@univ-fcomte.fr	0381668232	Hematology
10	Maillard	Natacha	Poitiers	France	CHU Poitiers	natacha.maillard@chu-poitiers.fr	0549444807	Hematology
11	Reman	Oumedaly	Caen	France	CHU Caen	Reman-o@chu-caen.fr	0231272546	Hematology
12	Fegueux	Nathalie	Montpellier	France	CHU Montpellier	n-fegueux@chu-montpellier.fr	0467338079	Hematology
13	Turlure	Pascal	Limoges	France	CHU Limoges	pascal.turlure@chu-limoges.fr	0555056642	Hematology
14	Cornillon	Jérôme	Saint Etienne	France	Institut de Cancérologie Lucien Neuwirth	jerome.cornillon@icloire.fr	0477917060	Hematology
15	Charbonnier	Amandine	Amiens	France	CHU Amiens	charbonnier.amandine@chu-amiens.fr		Hematology
16	Lioure	Bruno	Strasbourg	France	CHRU Strasbourg	bruno.lioure@chru-strasbourg.fr	0388127676	Hematology
17	Contentin	Nathalie	Rouen	France	Centre Henri Becquerel	nathalie.contentin@chb.unicancer.fr		Hematology
18	Bulabois	Claude Eric	Grenoble	France	CHU Grenoble	CEBulabois@chu-grenoble.fr	0476765755	Hematology
19	Clément	Laurence	Nancy	France	CHU Nancy	l.clement@chu-nancy.fr		Hematology
20	Bay	Jacques Olivier	Clermont Ferrand	France	CHU Clermont Ferrand	jobay@chu-clermontferrand.fr	0473750065	Hematology

17.2 Appendix 2: Leucémies aiguës myéloïdes et pathologies apparentées selon la classification OMS 2008 {Vardiman, 2009 #800}

LAM avec anomalies génétiques récurrentes
- LAM avec t(8;21)(q22;q22); RUNX1-RUNX1T1
- LAM avec inv(16)(p13.1q22) ou t((16;16)(p13.1;q22); CBFB-MYH11
- Leucémie aiguë promyélocytaire avec t(15;17)(q22;q12); PML-RARA
- LAM avec t(9;11)(p22;q23); MLLT3-MLL
- LAM avec t(6;9)(p23;q34); DEK-NUP214
- LAM avec inv(3)(q21q26.2) ou t(3;3)(q21;q26.2); RPN1-EVI1
- LAM (megacaryoblastique) avec t(1;22)(p13;q13); RBM15-MKL1
- LAM avec mutation NPM1*
- LAM avec mutation CEBPA*

LAM avec caractéristiques myélodysplasiques

Hémopathies myéloïdes induites par une thérapeutique

LAM sans spécification
- LAM avec différenciation minimale (LAM0)
- LAM sans maturation (LAM1)
- LAM avec maturation (LAM2)
- Leucémie aiguë myélomonocytaire (LAM4)
- Leucémie aiguë monoblastique/monocytaire (LAM5a et 5b)
- Leucémie aiguë érythroblastique (LAM6)
  - Leucémie érythroblastique pure (LAM6a)
  - Erythroleucémie, érythroïde/myeloïde (LAM6b)
- Leucémie aiguë mégacaryoblastique
- Leucémie aiguë à basophiles
- Panmyélose aiguë avec myélofibrose

Sarcome granulocytaire

Myéprolifération des trisomies 21 constitutionnelles
- Myélopoïèse transitoirement anormale
- LAM associée aux trisomies 21 constitutionnelles

Leucémie aiguë à cellules dendritiques plasmocytoïdes

*entités provisoires

17.3 . Appendix 3: MDS IPSS Scoring system

Calcul du score pronostic des syndromes myélodysplasiques :

Facteur pronostic	Critère		Score
Blastes médullaires	< 5% 5-10% 11-20% 21-30%		0 0,5 1,5 2
Caryotype	Favorable : normal ou 5q-, 20q-, -Y (anomalie isolée)		0
	Intermédiaire : toutes les autres anomalies		0,5
	Défavorables : -7, +8, complexe (>3 anomalies)		1
Cytopénies : 13.	-PNN<1,8 G/L -Hb < 10 g/dL -plaquettes < 100 G/L	0 ou 1 2 ou 3	0 0,5

17.4 Appendix 4: GVHD clinical gradation

ECHELLE DE COTATION DE LA REACTION DU GREFFON CONTRE L'HOTE (GVH)

11.i.A. GVH AIGUË : STADES CLINIQUES

SURFACE CORPORELLE (%)	Jambe	Cuisse	Tête	OGE	Cou	Tronc	Fesse	Bras	Avant-Bras	Main	Pied
Adulte : Total	7	9,5	7	1	2	26	2,5	4	3	3	3,5
Ant ou post :	3,5	4,75	3,5		1	13		2	1,5	1,5	1,75

STADES CLINIQUES	**PEAU :** Éruption maculopapuleuse	**INTESTIN :** Volume Diarrhée		**FOIE :** Bilirubine	
		Adulte	Enfant	**µmol/l**	mg/dl
+	< **25**% S.C.	> **500** ml/j ***ou*** nausées, anorexie, vomissements*	7-14 ml/kg	**34-50**	2-3,5
+ +	25-**50**% S.C.	> **1000** ml/j	14-21 ml/kg	**51-102**	3,5-7,9
+ + +	> **50%** S.C.	> **1500** ml/j	21-28 ml/kg	**103-255**	8-15
+ + + +	Érythrodermie généralisée. Bulles-desquamation	> **1500 ml/j et** douleurs abdominales ± iléus	> 28 ml/kg	**> 255**	> 15

**: confirmation histologique pour la GVH du tube digestif haut*

GRADE GVH AIGUE	**STADES CLINIQUES**		
Glücksberg-Thomas*	**Peau**	**Intestin**	**Foie**
I	1	0	0
I	2	0	0
II	0-2	1	0-1
II	0-2	0-1	1
II	3	1	0-1
II	3	0-1	1
II	3	0	0
III	0-2	2	0-2
III	0-2	0-2	2
III	3	0-3	2-3
III	3	2-3	0-3
III	0-3	0-3	4
IV	0-3	4	0-4
IV	4	0-4	0-4

** : Selon Glücksberg, (1) une GVH cotée de II à IV et ne touchant qu'un seul organe doit être confirmée histologiquement, (2) une AEG avec Karnofsky < 30 % = grade IV.*

11.i.B. GVH CHRONIQUE

Limitée : Atteinte cutanée localisée et/ou atteinte hépatique due à la GVH chronique

Extensive : Atteinte cutanée généralisée ou GVH chronique limitée
Plus :

a. Hépatite chronique agressive ou cirrhose
ou b. Atteinte oculaire (syndrome sec)
ou c. Atteinte salivaire ou de la muqueuse buccale
ou d. Atteinte d'un autre organe

17.5 Appendix 5: Evaluation of performans status according to the classification of Karnofsky or the ECOG scale and evaluation of co-morbidities according to the SORROR index.

A. **EVALUATION DE L'ETAT GENERAL EN FONCTION DE LA CLASSIFICATION DE KARNOFSKY ET DE L'ECHELLE DE VALEUR DE L'ECOG**

ETAT GENERAL	ECHELLE KARNOFSKY	**ECOG**	ETAT GENERAL
Normal, pas de plaintes.	100	**0**	Activité normale, sans restriction.
Activité normale. Signes ou symptômes mineurs de la maladie. Activité normale avec efforts.	90 80	**1**	Restreint pour des activités physiques importantes mais patient ambulatoire et capable de fournir un travail léger.
Capable de se prendre en charge, mais incapable d'avoir une activité normale ou de travailler. Nécessite occasionnellement de l'aide, mais capable de subvenir à la plupart de ses besoins.	70 60	**2**	Ambulatoire et capable de se prendre en charge, mais incapable de fournir un travail pendant plus 50% de son temps.
Nécessite aide et soins médicaux fréquents. Nécessite soins médicaux et aide importante.	50 40	**3**	Capacité de prise en charge propre beaucoup plus limitée. Passe plus de 50 % de son temps au lit ou dans une chaise.
Sévèrement limité, grabataire. Indication d'hospitalisation, quoique la mort ne soit pas imminente. Gravement atteint. Hospitalisation nécessaire. Traitement symptomatique nécessaire	30 20	**4**	Complètement grabataire. Incapable de se prendre en charge. Le patient reste totalement couché au lit ou sur une chaise.

B. **Score de SORROR**

Score 1	**Définition**

Arythmie	Fibrillation auriculaire ou fluteur, arythmie ventriculaire
Cardiopathie	Coronaropathie (sous traitement médical : stent), insuffisance cardiaque, infarctus,
Maladies inflammatoires	Maladie de Crohn, …
Diabète	Sous insuline ou diabétiques oraux
Maladies cérébraux vasculaires	AIT, AVC
Affection psychiatrique	Dépression, anxiété sous traitement
Atteinte hépatique modérée	Bilirubine < 1,5N et transaminases < 2,5N.
Obésité	BMI > 35 kg /m²
Infection	Nécessitant la poursuite des antibiotiques après J0
Score 2	**Définition**
Rhumatologique	LEAD, PR, polymyosites, connectivites
Ulcère	Sous traitement
Atteinte rénale	Créatine > 177 µmol/l ou dialyse ou antécédent de greffe
Atteinte pulmonaire modéré	DLCO et/ou VEMS > 65 – 80% ou dyspnée au moindre effort
Score 3	**Définition**
Antécédents carcinologiques	Excluant les cancers de la peau hors mélanome
Maladies valvulaires	Excluant prolapsus mitral
Maladie pulmonaire sévère	DLCO et/ou VEMS ≤65 – 80% ou dyspnée de repos ou malade sous oxygène
Malade hépatique sévère	Cirrhose, bilirubine > 1,5N, ou transat > 2,5N

17.6

17.6 Appendix 6: Evaluation of Quality of life FACT-BMT (version 4))

Evaluation prospective de la qualité de vie des patients recevant une allogreffés de cellules souches hématopoïétique avec un conditionnement à toxicité réduite

Enregistrement du patient

Identification du centre :

Code (CIC):
Hôpital d'origine:
Unité:
Médecin responsable:
Téléphone:
Fax:
E-mail:

Date d'enregistrement:
(jj/mm/aaaa)

Identification du patient:

Initial du nom :
Initiale du prénom:

Date de naissance (jj/mmm/aaaa) :

Sexe: femme
Homme

Date attendue de l'allogreffe (jj/mm/aaaa):
Conditionnement prévu:

Consentement éclair signé du patient
Patient apte à comprendre et remplir les questionnaires

Remarques:

Questionnaire

RENSEIGNEMENTS SOCIO DÉMOGRAPHIQUES

Pourriez vous répondre à ce questionnaire socio-démographique. Certaines questions peuvent apparaître personnelles mais sont nécessaires à notre analyse. Nous vous rappelons que toutes vos réponses seront traitées de manière strictement confidentielle.

1. Date du jour |_|_|_|_|_|_|
2. Date de Naissance |_|_|_|_|_|_| 3. Sexe F H
4. Etes-vous ?
   - marié(e) 1
   - veuf / veuve 2
   - divorcée(e) 3
   - célibataire 4
5. Actuellement, vivez-vous en couple ? oui non
6. Quel est le niveau d'étude ou le diplôme le plus élevé que vous avez atteint?
   - aucun diplôme 1
   - école primaire – certificat d'étude 2
   - certificat d'aptitude professionnelle (CAP) 3
   - secondaire niveau 3ième – brevet – brevet professionnel 4
   - baccalauréat 5
   - études universitaires – diplômes de l'enseignement supérieur 6
7. Quelle est votre profession ? ……
   (répondre en clair le plus précisément possible)
8. Actuellement, êtes-vous ?
   - En arrêt maladie 1
   - en activité 2
   - au chômage 3
   - à la retraite 4
   - en activité au foyer 5
   - autre 6
9. Avez-vous des enfants ? oui non
   Si oui, combien ? |_|_|
   actuellement combien sont à votre charge ? |_|_|

FACT-BMT (4ÈME VERSION)

Initiales du receveur : |__|__|__| **Nº d'étude du receveur :** |__|__|__|__|

Vous trouverez ci-dessous une liste de commentaires que d'autres patients, atteints de la même maladie, ont jugé importants. **Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.**

BIEN-ÊTRE PHYSIQUE		Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GP1	Je manque d'énergie ……	0	1	2	3	4
GP2	J'ai des nausées ……	0	1	2	3	4
GP3	À cause de mon état physique, j'ai du mal à répondre aux besoins de ma famille …	0	1	2	3	4
GP4	J'ai des douleurs ……	0	1	2	3	4
GP5	Je suis dérangé(e) par les effets secondaires du traitement ……	0	1	2	3	4
GP6	Je me sens malade ……	0	1	2	3	4
GP7	Je suis obligé(e) de rester alité(e)……	0	1	2	3	4

Total du score GP : ……..

BIEN-ÊTRE FAMILIAL/SOCIAL		Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
	Je me sens proche de mes amis ……	0	1	2	3	4
GS2	Ma famille me soutient moralement …….	0	1	2	3	4
GS3	Mes amis me soutiennent ……...	0	1	2	3	4
GS4	Ma famille a accepté ma maladie ……	0	1	2	3	4
GS5	Je suis satisfait(e) de la communication avec ma famille au sujet de ma maladie	0	1	2	3	4
GS6	Je me sens proche de mon (ma) partenaire (ou de la personne qui est mon principal soutien) ……..	0	1	2	3	4
Q1	*Quel que soit votre niveau actuel d'activité sexuelle en ce moment, pouvez-vous répondre à la question suivante. Si vous préférez ne pas y répondre, cochez cette case et passez à la section suivante.*					
GS7	Je suis satisfait(e) de ma vie sexuelle ……	0	1	2	3	4

Total du score GS : ……..

Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.

	BIEN-ÊTRE ÉMOTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GE1	Je me sens triste ……..……	**0**	**1**	**2**	**3**	**4**
GE2	Je suis satisfait(e) de la façon dont je fais face à ma maladie ……	**0**	**1**	**2**	**3**	**4**
GE3	Je perds l'espoir dans le combat contre ma maladie ……	**0**	**1**	**2**	**3**	**4**
GE4	Je me sens nerveux (nerveuse)……	**0**	**1**	**2**	**3**	**4**
GE5	Je suis préoccupé(e) par l'idée de mourir .	**0**	**1**	**2**	**3**	**4**
GE6	J'ai peur que mon état s'aggrave……..	**0**	**1**	**2**	**3**	**4**

Total du score GE : ……..

	BIEN-ÊTRE FONCTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GF1	Je me sens capable de travailler (y compris le travail à la maison)……	**0**	**1**	**2**	**3**	**4**
GF2	Mon travail (y compris le travail à la maison) me donne de la satisfaction……	**0**	**1**	**2**	**3**	**4**
GF3	Je suis capable de profiter de la vie ……	**0**	**1**	**2**	**3**	**4**
GF4	J'ai accepté ma maladie ……	**0**	**1**	**2**	**3**	**4**
GF5	Je dors bien……	**0**	**1**	**2**	**3**	**4**
GF6	J'apprécie mes loisirs habituels ……...	**0**	**1**	**2**	**3**	**4**
GF7	Je suis satisfait(e) de ma qualité de vie actuelle ……	**0**	**1**	**2**	**3**	**4**

Total du score GF : ……..

Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.

	AUTRES SUJETS D'INQUIÉTUDE	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
BMT1	Je m'inquiète de ne pas pouvoir continuer à travailler (y compris le travail à la maison)…	**0**	**1**	**2**	**3**	**4**
BMT2	Je me sens distant(e) des autres …….	**0**	**1**	**2**	**3**	**4**
BMT3	J'ai peur que la greffe ne réussisse pas ……	**0**	**1**	**2**	**3**	**4**
BMT4	Les effets du traitement sont pires que ce que j'imaginais ……	**0**	**1**	**2**	**3**	**4**
C6	J'ai bon appétit …….	**0**	**1**	**2**	**3**	**4**
C7	Je suis satisfait(e) de mon apparence physique…… …	**0**	**1**	**2**	**3**	**4**
BMT5	Je peux me débrouiller seul(e)……..	**0**	**1**	**2**	**3**	**4**
BMT6	Je me sens fatigué(e) facilement ……	**0**	**1**	**2**	**3**	**4**
BL4	Le sexe m'intéresse ……	**0**	**1**	**2**	**3**	**4**
BMT7	J'ai peur de ne plus pouvoir avoir d'enfants..	**0**	**1**	**2**	**3**	**4**
BMT8	J'ai confiance en mes infirmières(iers)……	**0**	**1**	**2**	**3**	**4**
BMT9	Je regrette d'avoir eu une greffe de la moelle osseuse …….	**0**	**1**	**2**	**3**	**4**
BMT 10	J'ai de la mémoire ……	**0**	**1**	**2**	**3**	**4**
Br1	Je suis capable de me concentrer …….	**0**	**1**	**2**	**3**	**4**
BMT 11	J'ai fréquemment des rhumes ou des infections ……..	**0**	**1**	**2**	**3**	**4**
BMT 12	Je vois trouble …….	**0**	**1**	**2**	**3**	**4**
BMT 13	Je suis gêné(e) par un changement de goût des aliments…….	**0**	**1**	**2**	**3**	**4**
BMT 14	J'ai des tremblements ……..	**0**	**1**	**2**	**3**	**4**
B1	J'ai le souffle court ……..	**0**	**1**	**2**	**3**	**4**
BMT 15	Je suis gêné(e) par des problèmes de peau (éruptions démangeaisons)……	**0**	**1**	**2**	**3**	**4**
BMT 16	J'ai du mal à aller à la selle ……	**0**	**1**	**2**	**3**	**4**
BMT 17	Ma maladie est une lourde épreuve pour ma famille proche ……..	**0**	**1**	**2**	**3**	**4**
BMT 18	Le coût du traitement est un fardeau pour moi	**0**	**1**	**2**	**3**	**4**

et pour ma famille
……

Date d'achèvement : |__|__| |__|__|__| |__|__|__|__|
JJ MMM AAAA

Rempli par :≤ le sujet *(version papier*) ≤ le sujet *(en ligne)*
≤ le coordonnateur de l'étude (entretien téléphonique)

17.7 Appendix 7 : Reconstitution immunitaire et Etude des mismatch KIR

A. Reconstitution immunitaire post-greffe

Les patients inclus dans l'étude seront informés et donneront leur consentement au moment de la consultation pré-greffe.
Un prélèvement sanguin est réalisé à J30, J60, J90, 6 mois et 1 an après la greffe.

A chaque point, 40 ml de sang sont prélevés et acheminés dans les 24 heures qui suivent au centre de recherche biologique (CRB) de l'URC-Est à l'hôpital Saint Antoine.

Les PBMC seront séparées du sang périphérique par technique du FICOLL et congelées au CRB.

Les analyses phénotypiques seront réalisées dans un deuxième temps dans le laboratoire du Pr Mothy à l'hôpital Saint Antoine et consisteront en l'analyse des différents sous types lymphocytaires par cytométrie en flux avec les marqueurs de surface suivants :

-lymphocytes B: CD3, CD56, CD19, CD20, CD5 (B produisant de l'IL10)

-lymphocytes NK : CD3, CD56, NKG2A, KIR2DL1/2/3, LIR-1 (récepteurs inhibiteurs), NKG2D, NKp30, NKp44, NKp46 (récepteurs activateurs)

-lymphocytes T (naifs/mémoires): CD3, CD4, CD8, CD45RA (naifs), CD45RO (mémoires), CCR7 (central mémoire/effecteur mémoire), HLADR (activation), CD122 et CD95 (TsCM)

-lymphocytes T (orientation Th1/Th2/TH17): CD3, CD4, CD8, CD25, CD45RO, CCR4, CCR6 (Th17), CXCR3 (Th1), CRTH2 (Th2)

-lymphocytes T régulateurs : CD3, CD4, CD25, FoxP3, CD45RA, CD127, Ki67, CD39

-lymphocytes iNKT : CD3, CD4, CD8, CD56, Tétramère CD1d, CD161, CD69 (activation), CD31 (marqueur d'émigrant thymique récent)

-Cellules dendritiques (cDC et pDC): CD3, CD19, CD56, CD16, CD1c, CD11c, CD123, HLA DR, CD141 (cDC : CD3-, CD56-, CD19-, CD14-, HLADR+, CD1c+, CD123low, BDCA2- versus pDC : CD3-, CD56-, CD19-, CD14-, HLADR+, CD1c-, CD123high, BDCA2+)

A 3, 6 et 12 mois, si le nombre de cellules le permet, nous chercherons à analyser les réponses T anti-CMV et EBV par technique ELISPOT ou par tétramères HLA restreints pour les molécules HLA les plus fréquentes (disponibles en HLA A02 :01, 11 :01, 07 :02, 24 :02, 35 :01, 08 :01).

B. Etude des mismatch KIR des unités de sang placentaire :

Un aliquot de chaque unité de sang placentaire habituellement conservé dans les unités de thérapie cellulaire sera transmis congelé au centre de recherche biologique (CRB) de l'URC-Est à l'hôpital Saint Antoine à la fin de l'étude.

Ces cellules seront utilisées pour analyser les mismatch KIR entre cellules du greffon et receveur.

Ces analyses seront réalisées dans le laboratoire du Dr Vincent Vieillard à la Pitié Salpétrière.

Cette étude se fera à partir des prélèvements d'ADN, qui pourra soit avoir été extrait précédemment et congelé, soit extrait à partir de sang total placentaire en utilisant le QIAamp DNA mini kit de Qiagen.

Le profil d'expression des gènes KIR sera étudié avec le KIR Typing Kit de Myltenyi Biotec.

La présence ou l'absence des gènes KIR est analysée par la technique de PCR utilisant les sequence-specific primers (SSPs) permettant de détecter 15 gènes KIR inhibiteurs et activateurs (et leurs variants) ainsi que 2 pseudo-gènes.
Les gènes étudiés sont les suivants : KIR2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DL5A, 2DL5B, 3DL1, 3DL2, 3DL3 ; KIR2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DS1 ; KIR2DP1 ; KIR3DP1.

17.8 Appendix 8: Toxicity scale CTCAE V4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

17.9 Appendix 9: Chimerism analysis

Définition des marqueurs génétiques

- Les marqueurs utilisés le plus fréquemment par le laboratoire sont des SNPs (single nucleotide polymorphisms), des STRs (short tandem repeats) et des VNTRs (variable number of tandems repeats).
- **Avant toute allogreffe, il est indispensable de définir le ou les marqueurs génétiques** pour le(s)quel(s) il existe une différence entre le donneur et le receveur. Ce polymorphisme allélique permet d'analyser le niveau du chimérisme chez le malade greffé. Le principe est de détecter la réapparition de cellules «d'origine receveur» après la greffe.
- Le marqueur génétique permettant de définir et de suivre le chimérisme est choisi en fonction de plusieurs critères : une différence de polymorphisme entre le donneur et le receveur, le type de marqueur (préférence généralement donnée aux SNPs ou aux STRs), la configuration du polymorphisme entre le donneur et le receveur, l'adéquation entre les quantités réelles d'ADN du donneur et du receveur des mélanges artificiels constitués pour construire la courbe étalon (cf. infra) et les quantifications obtenues avec le(s) marqueur(s). Dans la configuration optimale, le seuil de détection de la méthode est ≤ à 1%.

Principe de la méthode d'analyse du chimérisme

L'analyse du chimérisme est réalisée par PCR quantitative en temps réel ou PCR compétitive. Chez le receveur après greffe, pour la PCR compétitive, la détermination **semi-quantitative du pourcentage** de cellules du receveur et du donneur est obtenue en utilisant une droite étalon construite à partir de points correspondants à des quantités variables et connues d'ADN du donneur et du receveur ; pour la PCR quantitative en temps réel, la détermination quantitative du pourcentage de cellules du receveur et du donneur est obtenue par la méthode des « delta (delta CT) »

Origine des cellules

L'analyse du chimérisme est réalisée sur des sous populations cellulaires obtenues à partir des cellules du **sang périphérique** des malades greffés.

Un effort de consensus sur les techniques de tri cellulaire est réalisé actuellement au sein du Groupe Français d'Etudes sur le chimérisme (GEC) afin d'harmoniser les résultats entre les centres biologiques. Les recommandations sont les suivantes :

- après séparation des globules blancs sur «buffy coat» (afin de limiter au maximum la perte cellulaire), les différentes sous populations cellulaires sont triées par des anticorps monoclonaux fixés à des billes magnétiques (Dynal®, par exemple).
- Les sous populations suivantes seront étudiées :
  - **Lymphocytes T** : obtenus en utilisant un mélange de billes portant les anticorps anti-CD4 et CD8 ou CD3.

- L'enrichissement des sous-populations est contrôlé en cytométrie de flux 4 couleurs en utilisant l'ensemble des anticorps monoclonaux suivants : anticorps anti-CD3, anticorps anti-CD15, anticorps anti-CD45, anticorps anti-CD56. Dans le cas des LLC B, l'anticorps anti-CD19 ou CD20 (en fonction du phénotype des cellules tumorales) sera également utilisé. Au sein de la sous-population cellulaire triée, la contamination par des cellules non désirées est analysée sans fenêtrage, en excluant les débris cellulaires. L'enrichissement doit être ≥ à 95%.

  - **Volume de sang nécessaire et conditions de prélèvements**
  - **20 à 25 ml** de sang périphérique sont nécessaires *pour* ***chaque*** **point d'analyse**.
  - Le sang doit être prélevé sur **EDTA** ou **ACD** (**jamais sur Héparine**).
  - Pour des raisons de sécurité le prélèvement sera effectué **sur plusieurs tubes**

17.10 Appendix 10: Declaration of serious adverse events (SAE)

Fiche de déclaration d'événement indésirable grave

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une Recherche Biomédicale portant sur un Médicament ou produit assimilé**	**PARTIE RÉSERVÉE AU PROMOTEUR** **_ _ - DRRC 20 _ _ - _ _ _ _**

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99

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

1. Identification de la recherche

Acronyme : **TBF-Cord**

Code de la Recherche : P 131201

Autre référence (à compléter) :

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 Biomédicale (à compléter) : Reduced Toxicity Conditioning prior to Unrelated Cord Cell Transplantation for high risk myeloid malignancies

Risque : ☐ A ☐ B ☐ C ☐ D

Plan expérimental : ☐ Essai non comparatif

☐ Essai comparatif : ☐ Double aveugle ☐ Simple aveugle ☐ Ouvert ☐ Randomisé ☐ Non randomisé

2. Centre Investigateur

Nom de l'établissement : .....Hôpital saint Antoine.....
Ville et code postal : 75 Paris.....
Service : ... Service d'Hématologie et de thérapie cellulaire .....

Investigateur (nom/prénom) : .....Dr RUBIO Marie Thérèse.....
Tél: 01 49 28 26 21 Fax : 01 49 28 33 75

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

Date de greffe : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

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

.....
.....
.....
.....
.....
.....
.....

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG *(barrer l'encadré si traitement non débuté)* :

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Thiotepa	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

Busulfan	....	....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Fludarabine	....	....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Anti-thymocyte Globulin	....	....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Procédures et actes ajoutés par la recherche	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Immunosuppresseur : ………………………………………………	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Immunosuppresseur : ………………………………………………	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Immunosuppresseur : ………………………………………………	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

Cellules souches Hématopoïétiques (CSH) issues de sang de cordon administrées avant la survenue de l'évènement :

Nom du produit expérimental	Voie *(1)*	Nombre de cellules administrées	Heure de début	Heure de fin
USP 1		|__|__|,|__|__| X10 CNT/Kg avant décongélation |__|__|,|__|__| X10 CNT/kg après décongélation	|__|__| hh |__|__|min	|__|__| hh |__|__|min
USP2		|__|__|,|__|__| X10 CNT/Kg avant décongélation |__|__|,|__|__| X10 CNT/kg après décongélation	|__|__| h h |__|__|min	|__|__| hh |__|__|min

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants*** ⇨ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non ***ou barrer l'encadré si non applicable) :***

Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie(1)	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
………………………………………………	……………………	………	………	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
………………………………………………	……………………	………	………	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
………………………………………………	……………………	………	………	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
………………………………………………	……………………	………	………	|__|__| |__|__| |__|__|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

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

Acronyme : **TBF CORD**

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

PARTIE RÉSERVÉE AU PROMOTEUR
_ _ - DRRC 20 _ _ - _ _ _ _

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire
……………………………………………………
……………………………………………………
……………………………………………………

Organe(s) concerné(s) :
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………

Symptôme(s) :
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………
……………………………………………………

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels ……………………………………………………
……………………………………………………
……………………………………………………

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

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

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

L'évènement a-t-il conduit à une <u>interruption du/des ME/produit assimilé(s) à l'étude</u> ?

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

L'arrêt de traitement a été : ○ Provisoire ○ Définitif

Le cas échéant, date de reprise du traitement à l'étude : |__|__| |__|__| |_2_|_0_|__|__|

Récidive de l'EIG après ré-administration : ○ Non ○ Oui - Date : |__|__| |__|__| |_2_|_0_|__|__|

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

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

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

Correspondant Local de Biovigilance informé oui ☐ non ☐

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

Gravité de sévérité selon l'échelle CTCAE :

☐ 1ère(s) ☐ 2ème(s) ☐ 3ème(s) ☐ 4ème(s) médicalement significatif(s), préciser :

En cas d'infection :

GREFIG : Grade I ☐ Grade II ☐ Grade III ☐

En cas de GVH :

Glucksberg-Thomas : Stade 1 ☐ Stade2 ☐ Stade 3 ☐ Stade 4 ☐

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
- ○ Aggravation
- ○ Amélioration

☐ **Guérison :**
- ○ sans séquelles
- ○ avec séquelles, préciser lesquelles :

Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

|__|__| |__|__|
hh min

Des mesures symptomatiques ont été prises :

☐ Non ☐ Oui Si oui, préciser :

8. Autre(s) étiologie(s) envisagée(s) :

☐ Non ☐ Oui Si oui, préciser :

9. Examen(s) complémentaire(s) réalisé(s) :

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

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

<u>Lié à la recherche biomédicale</u> :

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

Thiotepa	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse
Fludararabine	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse
Busulfan	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse
Anti-thymocyte Globulin	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse

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

Greffe de sang de cordon :	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse
Immunosuppresseur :	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse
Immunosuppresseur :	☐ Relation certaine	☐ Relation plausible	☐ Relation douteuse

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

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

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

○ **autre, préciser :** .....

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

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS	Formulaire
	Suivi d'une grossesse apparue au cours d'une recherche biomédicale	*Version n°2-1* *Date d'application : 26/03/2014*

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par <u>télécopie</u> au +33 (0)1 44 84 17 99

DRRC 20 _ _ - _ _ _ _
(N° unique interne au DRCD)

1. Identification de la recherche

Acronyme *(à compléter)* :
Code P *(à compléter)* :

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

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

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

Titre complet de la Recherche Biomédicale *(à compléter)* :

2. Identification du centre Investigateur

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

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

3. Identification de la personne présentant une grossesse

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

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

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

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

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

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

Expositions : Préciser si exposition au tabac (paquets/année), à l'alcool (unités OH), à des drogues et autres expositions.
Préciser si l'exposition est antérieure à la grossesse, poursuivie ou arrêtée (mentionner la date d'arrêt le cas échéant).

4. Antécédents maternels

Médicaux :

Chirurgicaux :

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

5. Médicament(s) expérimental(aux) administré(s) pendant la grossesse ou s'il s'agit une exposition paternelle ***(barrer la mention inutile)***

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

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

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |_2_|_0_|__|__|		
	|__|__| |__|__| |_2_|_0_|__|__|		

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

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		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser :

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

9. Grossesse en cours ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse)

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

☐ Fausse couche spontanée → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :	Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J
☐ Grossesse extra-utérine	Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J
☐ Interruption de grossesse → Raison : → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :	Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J
☐ Accouchement ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne	Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

Souffrance fœtale : ☐ Non ☐ Oui, précisez :

Placenta normal : ☐ Oui ☐ Non, précisez :

Liquide amniotique : ☐ clair ☐ autre, précisez :

Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

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

Sexe : ☐ Masculin ☐ Féminin

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

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

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

Pathologie néonatale non malformative : ☐ Non ☐ Oui, précisez :

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

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

17.11 Appendix 11: circuit pharmaceutique – RCP

http://www.sante.gouv.fr/medicaments,1969.html

Traçabilité alternative hospitalière

Numéro EudraCT : **2014-002109-39**

Objet de l'addendum

La recherche porte sur des médicaments utilisés dans les conditions ouvrant droit au remboursement par les caisses d'assurance maladie (en application de l'article L1121-16-1 du code de la santé publique).
Le promoteur est institutionnel, la recherche a pour objectif de comparer des stratégies thérapeutiques utilisées dans le cadre du soin, et les médicaments utilisés dans le cadre de cette recherche bénéficient d'une AMM et sont utilisés conformément à leur AMM : la fourniture des produits peut donc être déléguée par le promoteur aux centres participant à la recherche.

Gestions des médicaments expérimentaux

L'approvisionnement, le stockage, la préparation, la dispensation, la destruction des médicaments expérimentaux seront réalisés conformément au circuit du médicament propre à la PUI de chaque centre (en application de l'article L. 5126-5 du code de la santé publique).

La PUI se chargera également de mener ou de participer à toute action d'information sur ces médicaments : rappels de lot, pharmacovigilance, sécurisation du circuit du médicament.

Etiquetage des médicaments expérimentaux

Le promoteur fournira des contre-étiquettes conformes aux mentions règlementaires des BPF, pour compléter l'étiquetage classique des poches de chimiothérapies fourni par les PUI. Parallèlement une carte patient sera remise à chaque participant à l'étude (cf modèle ci-dessous).

Traçabilité

La traçabilité de la préparation du médicament sera assurée par le dossier de préparation du médicament de la PUI.

Une copie de cette fiche de fabrication sera effectuée par le TEC/investigateur qui récupèrera également une copie de la fiche d'administration du médicament : celles –ci seront conservées dans le dossier du patient.
L'ensemble de ces éléments sera monitoré par l'ARC.

Carte patient

Merci de garder cette carte en permanence avec vous.

Cette carte est à présenter à tout médecin ou professionnel de santé en dehors de visites prévues au protocole.

Nom : …….

Prénom : …….

Je participe à l'étude clinique : TBF-Cord

" Reduced Toxicity Conditioning prior to Unrelated Cord Cell Transplantation for high risk myeloid malignancies ".

Dont le promoteur est.

l'Assistance Publique Hôpitaux de Paris, DRCD

Ma chimiothérapie a débuté le _ _ / _ _ / _ _ _ _

Je suis suivi(e) par le Dr……..…….

A l'Hôpital ……..…….

Tél. : ……

17.12 Appendix 12 : Circuit de signalement et de déclaration des incidents et effets indésirables du donneur

17.13 Appendix 13: Study summary in French

Introduction :

L'allogreffe de sang placentaire (CBT) est une immunothérapie potentiellement curative dans les hémopathies malignes dont les hémopathies myéloides à haut risque. Chez l'adulte. un taux de mortalité non liée à la rechute (NRM) de 40% observé après CBT réalisées avec un conditionnement myéloablatif a conduit au développement de CBT avec des conditionnements à intensité réduite (RIC). Le précédent protocole national français de RIC CBT (protocole Minicord - NCT00797758) avait en effet montré une réduction de la NRM mais un risque élevé de rechute (>30% à un an). Le développement de conditionnements à toxicité réduite (RTC), plus intensifs que les RIC, pourrait permettre d'améliorer les résultats en maintenant une NRM acceptable tout en réduisant le risque de rechute. Par ailleurs, la problématique de non prise des CBT doit être considérée. Les RIC CBT semblent nécessiter une irradiation corporelle totale à faible dose et/ou de serum anti-lymphocytaire (SAL) pour limiter ce risque. Dans le cadre d'allogreffes de cellules souches périphériques mobilisées par G-CSF, il a été établit que l'association de Fludarabine, SAL and doses intensifiées de Busulfan iv (9.6 mg/Kg total dose) (ClinicalTrials.gov Identifier: NCT00841724) peut être utilisée comme conditionnement à toxicité réduite. Il est cependant possible que ce conditionnement ne permette pas une prise de greffe de cellules de sang placentaire optimale. Le Thiotepa est un agent alkylant radiomimétique ayant une activité anti-leucémique, passant la barrière neuroméningée et favorisant la prise de greffe de cellules souches hématopoiétiques. Il a été associé à divers conditionnements de greffe sans en augmenter la toxicité, tout en favorisant la prise de greffe et réduisant potentiellement le risque de rechute. Nous proposons dans cette étude donc d'évaluer de manière prospective dans une cohorte de patient adulte présentant une hémopathie maligne à haut risque l'intérêt d'une allogreffe de sang placentaire avec un conditionnement à toxicité réduite associant Thiotepa, fludarabine, Busulfan IV et SAL.

Hypothèse :

Nous émettons l'hypothèse que ce conditionnement permettrait de réduire la NRM et de contrôler la maladie sous-jacente du fait de son potentiel cytotoxique anti-leucémique en attendant l'installation à plus long terme de la réponse immunologique anti-tumorale médiée par la greffe (effet GVL).

Méthodologie, plan expérimental :

Il s'agit d'une phase II multicentrique.

Critère d'évaluation principal :

NRM à 12 mois post-greffe

Critère(s) d'évaluation secondaire(s) :

Incidence de la prise de greffe

Incidence et sévérité de la GVH aigue et chronique

Incidence de rechute à 12 mois post-greffe
Survies sans rechute et globale
Reconstitution immunitaire post-greffe (étude ancillaire)
Qualité de vie post-greffe

Nombre de sujets nécessaires :
Sur la base d'une hypothèse de réduction de la NRM à 1 an post-greffe de 35% à 20%, 55 patients sont requis et 57 seront inclus.

Critères d'inclusion :
- Age entre 18 et 65 ans
- LAM de haut risque en RC1, LAM > RC1 ou Myélodysplasie avec score pronostic ≥ 2
- Absence de donneur familial ou fichier 10/10 ou 9/10 avec mismatch Cw
- 1 ou 2 unités de sang placentaire compatibles avec le receveur à 4, 5 ou 6/6 comprenant ≥ 4x107 TNC /kg avant congélation (≥ 2.5x107 TNC par USP en cas de double USP)
- Evaluation de l'état general OMS score ≤ 1 (cf. appendix 5)
- Fonction cardiaque adéquate (FEV≥45%)
- Fonctions respiratoires >50%
- Clairance de la créatinine >50 mL/min
- Transaminases < 4xN serum bilirubin < 2 x normal.
- Consentement éclairé signé
- Femme sous traitement progestatif si les menstruations sont persistantes.

Protocole thérapeutique :
Thiotepa 5 mg/Kg/jour à J-7 et J-6,
Fludarabine 40 mg/m²/jour de J-5 à J-2,
Busulfan IV 3.2 mg/Kg/jour à J-5, J-4 and J-3
Thymoglobuline 2.5 mg/Kg/jour à J-3 and J-2.
Prophylaxie de la GVH par ciclosporine and mycophenolate Mofetil.

Suivi des patients :
Les évaluations cliniques et biologiques auront lieu en pré-greffe puis à 1, 3, 6, 12 mois post-greffe et en fin d'étude.
Il est prévu de réaliser une étude ancillaire de reconstitution immunitaire approfondie.

Durée totale de l'étude : 36 mois

Période d'inclusion : 24 mois
Durée de participation pour un patient : 12 mois à 36 mois, en fonction de sa date d'inclusion
Nombre de centres participants : 20 centres d'allogreffe français au sein de la SFGM-TC

Les études statistiques seront réalisées en fin d'étude.

17.14 Appendix 14: Study chart

	<15 days before inclusion	Inclusion	Conditionning D-7 tà D-2	D 0	D30	D60	D100	6 months	12 months	End of study
identified CBU	x									
Informed consent	x	signature								
Medical history	x									
Physical exam (P. Status, infections)	x				x		x	x	x	x
Pregnancy test	x									
Viral Serologies	x									
WBC, liver and renal functions	x				x		x	x	x	x
Chest X-ray, lung function tests	x						x	x	x	x
ECG and echocardiogram	x								x	
Inclusion criteria validation		x								
Inclusion fax		x								
Disease evaluation (marrow aspiration +/- phenotyping +/- residual molecular disease)	x						x		x	
Fax for beginning conditioning			x							
CBT				x						
Chimerism	x				x		x		x	
Immune reconstitution	R				R	R	R	R	R	
Quality of life assessment		R			R		R	R	R	R
Send CB frozen aliquots *				R						R

Legend : R = Research / X= Care

CBU: cord blood unit, P. status: performans status, ECG : electrocardiogram, Disease evaluation: WBC counts + bone marrow aspiration +/- immunophenotyping +/- molecular biology (MRD).

*: one aliquot from each CBU kept in the cellular therapy departments involved in the study will be sent to the investigator's central collection laboratory at the end of the study for analyses of KIR mismatches.