Haplo-identical transplantation in patients with myelofibrosis – A phase 2 prospective multicentric prospective study

FIBRAPLO

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.0 of 25/10/2022
Project code number: APHP190648 /EUDRACT No.: 2019-003216-31

Coordinating Investigator : Dr Marie Robin
Service d'hématologie-greffe
Hôpital Saint-Louis
1 avenue Claude Vellefaux
75475 Paris Cedex
Tel : 01-42-49-47-24
Fax: 01-42-49-96-36
Email : marie.robin@aphp.fr

Sponsor:
AP-HP
and by delegation: Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI head office project advisor: Laura Blanchet
Tel. 01.44.84.17.32
Email : laura.blanchet@aphp.fr

Entity responsible for monitoring the trial:
Unité de Recherche Clinique (URC)
Hôpital Saint-Louis 1, avenue Claude Vellefaux, 75010 Paris
DRCI-URC (Clinical Research Unit)
project advisor: Chafia ABBOU-BENIHADDADENE
Tel. 01 42 38 53 22
Email: chafia.benihaddadene@paris7.jussieu.fr
Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint Louis 75010 PARIS

INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

Research code number: **APHP190648**

Title: Haplo-identical transplantation in patients with myelofibrosis- A phase 2 multicentric prospective study

FIBRAPLO

Version N°4.0 of 25/10/2022

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

Coordinating Investigator:
Dr Marie Robin
Service d'hématologie-greffe
Hôpital Saint-Louis
1 avenue Claude Vellefaux
75475 Paris
Tel: 01-42-49-47-24
Mail: marie.robin@aphp.fr

Date: 23/3/2023
Signature:

Sponsor
Assistance Publique-Hôpitaux de Paris
Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: 13 AVR. 2023
Signature:

Yannick VACHER
Responsable adjoint - Pôle Promotion
DRCI

TABLE OF CONTENTS

1 SUMMARY

Full title	Haplo-identical transplantation in patients with myelofibrosis A phase 2 prospective multicentric study
Acronym	FIBRAPLO
Coordinating Investigator	Dr Marie Robin Hôpital Saint-Louis, APHP, Paris
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	The only curative treatment in patients with primary or secondary myelofibrosis is allogeneic hematopoietic stem cells (HSCT). It has been reported that intermediate and higher risk patients according to international prognostic scores benefit from HSCT in terms of survival (Kröger *et al*, 2015). In 2013, we conducted in France a prospective trial testing the use of ruxolitinib before transplantation ("JAK-ALLO study" NCT01795677). Outcome of patients was better in patients transplanted with a matched sibling donor than an unrelated donor confirming other studies (Kröger *et al*, 2009; Rondelli *et al*, 2014). In the JAK-ALLO trial, acute GVHD incidence was high, often hyperacute and severe. Recently, the EBMT group has reported a registry study on familial haplo-identical transplantation (haplo) in patients with myelofibrosis (Raj *et al*, 2018). Post-transplant cyclophosphamide was used in 59% of cases. One-year overall survival (OS) and disease-free survival (DFS) were 61 and 58% which favorably compared to outcome after unrelated transplantation. Genova team has also reported impressive results after haplo-identical transplantation in their center (Bregante et al, 2015). Bregante et al have reported outcome of 2 cohorts transplanted from 2000 to 2010 and from 2011 to 2014. The main difference between the 2 periods is the more frequent use of haplo in the second period (54% versus 5%). Outcome was much better in the second period with OS at 70% versus 49% and authors suggest that this improvement is related to the best outcome among haplo transplantation. The improvement of outcome after haplo has been attributed to a better GVHD prophylaxis, especially with the use of post-transplant cyclophosphamide. Given the poor outcome after unrelated transplantation and especially in HLA mismatched unrelated setting and encouraging results in family haplo identical transplantation, this current study proposes to test haplo-identical transplantation in myelofibrosis patients without a matched related donor.

Main objective and primary endpoint	The main objective is disease-free survival and without rejection one year after haplo-identical transplantation in patients with primary or secondary myelofibrosis. The main criteria of judgement is disease- and rejection-free survival 12 months after HSCT.
Secondary objectives and endpoints	To assess -incidence of acute GVHD grade 2/4 at 100 days -incidence of acute GVHD grade 3 or 4 at 100 days -engraftment at 100 days -incidence of chronic GVHD at 12 months -non-relapse mortality at 12 months -overall survival at 12 months -relapse/progression incidence at 12 months -rejection incidence at 12 months -time to neutrophil engraftment at 100 days -time to platelet engraftment at 100 days -infection incidence at 100 days and at 12 months -cytokine profile during transplantation (day-7+/- 1 day , day 0 and day 7+/- 1 day) -impact of genetic alterations on overall survival at 12 months and non-relapse morality at 12 months
Design of the trial	This a phase 2 multicentric study
Population of trial subjects	Patients with a myelofibrosis who have no contraindication to transplant and who have an advanced disease by international scores could be proposed to the trial if they do not have an HLA-matched donor.
Inclusion criteria	✓ Patients aged between 18 and 70 years ✓ Primary myelofibrosis or myelofibrosis secondary to essential thrombocythemia or polycythemia Vera proven by marrow biopsy The myelofibrosis should combine at least 2 of the following criteria: o constitutional symptoms: weight loss > 10% in one year, fever (without infection), recurrent muscle, bone or join pains, extreme fatigue o anemia with hemoglobin < 10 gr/dL or red blood cell transfusion requirement o thrombocytopenia < 100 G/L o peripheral blast count > 1% at least found 2 times o white blood cell count > 25 G/L (before a cytoreductive treatment) o Karyotype: +8, -7/7q-, i(17q), -5, 5q-, 12p-, inv(3), 11q23 Performance status according to ECOG at 0, 1 or 2 With health insurance coverage Having signed a written informed consent

	✓ Women agreed to take nomegestrol acetate as contraception during and up to 6 months after treatment by treosulfan ✓ Men agreed not to conceive child during and up to 6 months after treatment by treosulfan
Exclusion criteria	✓ Myelofibrosis transformed into acute leukemia ✓ Poor performance status with ECOG 3 or more ✓ Cardiac failure with EF < or = 50% currently or in the past (even if corrected after treatment) ✓ Renal failure with creatininemia > 130 µmol/L or clearance < 50ml/min ✓ Respiratory function altered with vital capacity < 70% or forced expired volume < 70% ✓ Biological significant liver abnormalities; ASAT or ALAT> 2 x normal range, bilirubin > 1,5 x normal range ✓ HLA matched donor available ✓ Tutorship or curatorship ✓ Unwilling or unable to comply with the protocol ✓ Pregnant woman or breastfeeding ✓ Contraindications to treosulfan o Hypersensitivity to the active substance o Active non-controlled infectious disease o Fanconi anaemia and other DNA breakage repair disorders o Administration of live vaccine ✓ Contraindications or any circumstance that precludes the use of the drugs involved in the protocol (especially Thiotepa and Fludarabine)
Investigational medicinal product	Treosulfan, the investigational medicinal product, will be used in conditioning regimen for haplo-identical transplantation. Treosulfan, which received EU-wide approval for toxicity-reduced conditioning therapy prior to allogeneic haematopoietic stem cell transplantation on June 25 2019. will be provided by MEDAC. Treosuflan, in the conditioning regimen will be administered as followed : 10 gr/m^2 per day at -4, -3 and -2 (IV route) It will be used in combination with the standard association: Thiotepa 5 mg/kg on day -6 Fludarabine 30 mg/m^2 per day from day -5 to day -1 Therefore Thiotepa and Fludarabine, indissociable of Treosulfan will be also considered as medicinal product
Comparator treatment	*NA*

Interventions added for the trial	Haplo-identical transplantation with the use of Treosulfan, Thiotepa and Fludarabine in conditioning regimen. Additional plasma sample : 5 additional blood samples of 5 ml and 3 additional blood sample of 7 ml
Risks added by the trial	Risk D
Scope of the trial	Our goal is to show that haplo-identical HSCT using Thiotepa, Fludarabine in combination with Treosulfan gives acceptable results which can even be better than a transplantation from an HLA mismatched 9/10 donor, and close to a matched unrelated donor in patients with myelofibrosis
Number of subjects included	28
Number of sites	22
Duration of the trial	- inclusion period: 36 months - participation period (treatment+follow-up): 12 months Patients will be followed 24 months after transplantation to analyze the occurrence of GVHD and the survival or relapse status - total duration: 60 months
Number of enrolments expected per site and per month	**0 to 1 per month and per site**
Statistical analysis	The analysis will be based on the intent-to-treat basis, that is, including all patients whatever they were administered the treatment under study or not. *A sensitivity analysis will be performed in patients who will actually receive the graft.* Only patient consent withdrawals with positive report of not using their data, if any, will be excluded. Baseline summary statistics, namely percentages or median [interquartile range, IQR], will be performed. The right censored endpoint will be estimated using nonparametric methods. Kaplan Meier curves and cumulative incidence curves will be considered in case of non-informative or informative censoring based on the log-rank test or the Gray test, respectively. Adjustment on potential confounders will used the Cox proportional hazards models. Model assumptions will be checked using a test for proportional hazards and spline smoothing of residuals for the log-linearity assumption. Statistical analyses will be performed on SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.
Sources of funding for the trial	Industrial grant
Trial will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

Hematopoietic stem cell transplantation in patients with myelofibrosis

The only curative treatment in patients with primary or secondary myelofibrosis is allogeneic hematopoietic stem cells (HSCT). Many registry studies have reported outcome after transplantation with disease-free survival from 30 to 70% according to risk factors related to the patient, the disease and the type of transplantation (Kröger *et al*, 2009; Ballen *et al*, 2010; Deeg *et al*, 2003; Ditschkowski *et al*, 2012; Robin *et al*, 2011; Patriarca *et al*, 2008). Long-term outcome after HSCT has also reported minimal mortality after 2 years post-transplant, especially in younger patients (Robin *et al*, 2019). HSCT in patients with myelofibrosis has some specificities because patients usually have not received any chemotherapy before transplantation, they are transplanted with an uncontrolled disease exposing the patient to tumour lysis syndrome (5 to 10%) and no engraftment (5 to 10%). Secondary pancytopenia are also frequent after HSCT, usually transient (Alchalby *et al*, 2016). Furthermore, the management of their usual splenomegaly is still a matter of debate. Splenectomy has been reported as increasing relapse risk in one prospective trial but it was not confirmed by other study(Kröger *et al*, 2009). 10 to 40% of patients who received HSCT underwent a splenectomy, this proportion will possibly be lower using ruxolitinib before transplantation. Previous thrombosis, chronic hepatic disease as well as cardiac pulmonary hypertension are relatively frequent in these patients and should be taken into account when performing HSCT (Iurlo *et al*, 2015; Brabrand *et al*, 2019; Sciumè *et al*, 2017; Barraco *et al*, 2017; Tremblay *et al*, 2019). It has been reported that intermediate and higher risk patients according to international prognostic scores benefit from HSCT in terms of survival (Kröger *et al*, 2015). International recommendations from experts, confirm that HSCT should be performed in patients with higher risk and should be discussed in young patients who are at lower risk (intermediate-1). In 2013, we initiated in France a prospective trial testing the use of ruxolitinib before HSCT in patients with myelofibrosis (JAK-ALLO study NCT01795677). Outcome of patients was better in patients with a matched sibling donor than with an unrelated donor confirming previous prospective studies (Kröger *et al*, 2009; Rondelli *et al*, 2014; Gupta *et al*, 2019). In the JAK-ALLO trial, acute GVHD incidence was high (#70%), often hyperacute (#33%) and severe (grade 3-4 #44%). The majority of acute GVHD occurring after 9/10 HLA mismatched unrelated transplantation was grade 3-4 acute GVHD and mortality was in consequence high with disease-free survival at 1 year at 34% (compared 82% after HLA matched sibling donor).

Haplo-identical transplantation in patients with myelofibrosis

Haplo-identical transplantation has considerably progressed in the last years with better results and most frequent utilization in all countries. The use of post-transplant cyclosphosphamid has been reported safe and efficient to prevent GVHD without impairing engraftment (Luznik *et al*, 2012; Bashey *et al*, 2013; Raj *et al*, 2014). The majority of data concerns either acute leukemia or various diseases.

Recently, the EBMT group has reported a registry study on familial haplo-identical transplantation (haplo) in patients with myelofibrosis (Raj *et al*, 2018). Post-transplant cyclophosphamide was used in 59% of cases. One-year overall survival (OS) and disease-free survival (DFS) were 61 and 58% which compared favourably to outcome after unrelated transplantation. Genova team has also reported impressive results after haplo-identical transplantation in their center (Bregante et al, 2015). Bregante et al has reported outcome of 2 cohorts transplanted from 2000 to 2010 and from 2011 to 2014. The main difference between the 2 periods is the more frequent use of haplo in the second period (54% versus 5%). Outcome was much better in the second period with OS at 70% versus 49% and authors

suggest that this improvement is related to the best outcome among haplo transplantation. The improvement of outcome after haplo has been attributed to a better GVHD prophylaxis, especially with the use of post-transplant cyclophosphamide. Given the poor outcome after unrelated transplantation and especially in HLA mismatched unrelated setting and encouraging results in family haplo identical transplantation, this current study proposes to test haplo-identical transplantation in myelofibrosis patients without a matched related donor.

2.1 Hypothesis for the study

The hypothesis is that haplo-identical transplantation in patients with myelofibrosis gives better results (disease-free and rejection-free survival) that a transplantation from an HLA mismatched unrelated donor. We expect a disease- and rejection-free survival at one year at 55% with haplo as comparison to 30% in 9/10 mismatched unrelated donor.

2.2 Existing knowledge relating to the condition under investigation

Comparison between haplo and other alternative donor.

Twenty to thirty percent of patients will not have an HLA matched donor and the question of the best donor in these patients is still unresolved. Several options are available: mismatched unrelated donor (marrow, PB, cord blood) or mismatched related donor (haplo).

Several studies have reported that results of haplo using post-transplant cyclophosphamide are close to transplantation from an unrelated donor. Raiola et al has reported a registry comparison between HLA matched sibling donor (n=176), mismatched unrelated (n=43), matched unrelated (n=43), haplo (n=92) and mismatched unrelated cord blood (n=105) in patients transplanted for various haematological diseases (Raiola *et al*, 2014). In adjusted model, haplo gave similar OS than HLA matched sibling donor. Di stasi et al has also reported similar finding with survival at 57%, 45%, 41% after matched sibling, matched unrelated and haplo which were not significantly different (Di Stasi *et al*, 2014). A CIBMTR registry study has also compared transplantation from an HLA 8/8 matched unrelated donor (n=1982) to haplo (n=192) in patients with acute leukemia (Ciurea *et al*, 2015). Overall survival was considered similar (46% vs 44% after a reduced intensity conditioning regimen). In MDS patients, EBMT has reported that haplo and 9/10 mismatched unrelated donor gave similar outcome (Robin *et al*, 2019a). Finally, the potential equivalence of haplo to matched or mismatched donor is still a matter of debate (Shaw, 2017) and probably depends of many parameters which are the patient characteristics, the disease, the regimen, the GVHD prophylaxis, the age of donor, the richness of the graft …

In the setting of myelofibrosis patients, there is no comparison between haplo and other alternative transplantation yet. The EBMT registry study has reported a relative good outcome (Raj *et al*, 2018) with disease-free survival at 58% at one year. Genova team has also reported similar outcome in patients who received haplo for myelofibrosis (Bregante et al, 2015).

2.3 Summary of relevant pre-clinical and clinical trials

Justification of treosulfan the conditioning regimen

There is no recommended conditioning regimens for patients with myelofibrosis but usual conditioning regimens combined an alkylan and fludarabine. Prospective trials have either used fludarabine and melphalan (FM) or fludarabine and busulfan (FB2) at non-myelo-ablative dosage (Rondelli *et al*, 2014; Kröger *et al*, 2009; Gupta *et al*, 2019). The comparison of these 2 regimens showed that early toxicity was higher using melphalan but relapse rate was higher using busulfan. Outside the setting of myelofibrosis, registry comparisons also reported a

higher non-relapse mortality with FM than in FB2 but at the end a better control of the disease, especially in high risk acute myeloid leukemia (Kawamura *et al*, 2017).
Conditioning regimens including Treosulfan are usually considered as intermediate intensity regimens. A retrospective study has compared fludarabine-treosulfan (FT) to FB2 and FM showing that NRM was higher using FM and similar between FT and FB2 but FT was associated with the lowest rate of relapse (Yerushalmi *et al*, 2015). Another retrospective study compared FB2, FT and FB4 showing that day 100 NRM was low and similar in 3 arms (<15%) and a better anti-tumoral effect was seen with TF with better results in more advanced disease (Shimoni *et al*, 2012) which was also confirmed by others (Sakellari *et al*, 2017). Prospective trials have been conducted to assess the safety and efficiency of treosuflan based regimen, usually associated with fludarabine (FT). A phase 2 study has reported that NRM was low at 2 years (8%) in patients with acute leukemia or myelodysplastic syndrome (MDS) and 2-year DFS was 58%, and even 88% in patients without high risk cytogenetics which compared favourably to other regimens (Nemecek *et al*, 2011). Another phase II trial using 3 different doses (10, 12 or 14gr/m2) has reported a good tolerance and NRM at 18% at one year (Casper *et al*, 2010). 2-year OS was 60, 78 and 53% at 10, 12 or 14gr/m2. A prospective phase III study comparing FT and FB2 concluded to a superiority of FT in acute leukemia and MDS with a 64% EFS vs. 50% at 2 years. NRM was significantly lower in FT arm (12% vs 28%) (Beelen *et al*, 2017, 2019).
Thiotepa has been also been reported in association with FT with a good tolerance in various diseases (Baronciani *et al*, 2016; Choudhary *et al*, 2013).
In the setting of haplo, treosulfan has been also reported in combination with other drugs. Di Bartolomeo reported the association of cytarabine, endoxan and treosulfan 14gr/m2/day for 3 days with the use of post-transplant cyclophosphamide (11 patients among 80) (Di Bartolomeo *et al*, 2013). The type of conditioning regimen did not affect NRM in this study.
Generally, replacing Busulfan by Treosulfan appears as a good option by decreasing NRM justifying its use in the current trial.

Justification of the addition of fludarabine and thiotepa in conditioning regimen
Conditioning regimen initially developed by the Baltimore team consisted in 2 Gy total body irradiation (TBI) and fludarabine. This regimen gives low NRM but high relapse rate (Luznik *et al*, 2012). Conditioning regimen based on fludarabine-alkylan (melphalan or busulfan) and thiotepa have also been developed. Genova team has reported a regimen based on fludarabine-busulfan-thiotepa or fludarabine-TBI (high dose) in patients receiving haplo-identical transplantation. Engraftment with full donor chimerism was 90% and NRM was 18%. The busulfan dose was reduced to 1 or 2 days in order to decrease toxicity in fragile patients (Raiola *et al*, 2013). Conditioning associating fludarabine-melphalan and thiotepa have been also reported by MD Anderson group (Ciurea *et al*, 2012). Engraftment rate was > 90%, NRM at 1 year was 16% and OS was 64%.

Justification of source of stem cells in haplo-identical transplantation
It has been reported that acute GVHD incidence is lower using marrow as source of stem cells. However, engraftment is better using peripheral blood stem cells (PB). In the setting of reduced intensity conditioning regimen, overall survival and disease-free survival is not significantly different using marrow or peripheral stem cells (Bradstock *et al*, 2015; Castagna *et al*, 2014). O'donnel et al, reported similar GVHD incidence but higher relapse rate after non myelo-ablative regimen (O'Donnell *et al*, 2016). A CIBMTR study has compared 481 haplo from PB to 190 haplo from marrow. Acute GVHD and chronic GVHD incidences were higher using PB but relapse was higher using marrow. OS and DFS were similar using PB or marrow.
Myelofibrosis patients have a higher risk of no engraftment or poor engraftment justifying the choice of peripheral blood stem cells in this specific population. However, alternatively, marrow

can be used and has been proven as a safe source of stem cells in patients receiving an haplo transplant.

GVHD prophylaxis in haplo-identical transplantation
The use of post-transplant cyclophosphamide (PTC) has been initially reported by Baltimore team in T-cell repleted haplo-identical marrow. Engraftment was high (90%) with low rate GVHD and low rate NRM (<15%) (Luznik *et al*, 2012, 2010, 2008). It has been reproduced by many other teams as previously described (see above).

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

Patients with a myelofibrosis who have no contraindication for a transplantation and who have an advanced disease by international scores, ie age adjusted Dynamic International Prognostic System Score (DIPSS) in this trial (Passamonti *et al*, 2010), could be proposed to the trial if they do not have an HLA-matched donor.

Classification according to age adjusted DIPPS

Variable	Point	Score	Median overall survival (years)
Hemoglobine < 10 gr/dl	2	0	Not reached
White blood cells >25G/L	1	1-2	9.8
Blood blast ≥ 1%	1	3-4	4.8
Constitutional symptoms	1	>4	2.3

Indeed, the HSCT remains the only curative treatment and transplantation from an haplo identical donor appears as a relevant transplantation in view to the outcome observed in other myeloid malignancies. Several trials are raising the question of the possible equivalence between haplo and mismatched unrelated transplant (ALTERGREF NCT03250546) or haplo and matched unrelated transplant (MAC HAPLO MUD NCT 03655145) in France. Patients with myelofibrosis have some specificities with higher risk of acute GVHD, higher risk of graft rejection or poor engraftment and higher comorbidities like portal hypertension, portal thrombosis or liver dysfunction, justifying a specific study for them (see above).
Experience in haplo for patients with myelofibrosis remains limited as compared to patients with acute leukemia and only 60 cases in EBMT could be reported. For all these reasons: specificity of the disease, rare disease and new transplantation procedure, the trial has received the support of the French Society of transplantation (SFGM-TC) and the French group of myeloproliferative disease (FIM) with a majority of transplant centers kind to participate to the study.

2.5 Name and description of the investigational medicinal product

The investigational medicinal product is the Treosulfan.

Treosulfan, which received EU-wide approval for toxicity-reducing conditioning therapy prior to allogeneic haematopoietic stem cell transplantation on June 25 2019 will be provided by MEDAC. On 13 December 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Trecondi®, intended for the conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) (see Addendum)

Treosuflan, in the conditioning regimen will be administrated as followed
10 gr/m^2 per day -4, -3 and -2 IV route

In combination with:
Thiotepa 5 mg/kg on day -6
Fludarabine 30 mg/m^2 per day from day -5 to day -1

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

Treosulfan will be administered in intravenous over 2 hours 3 consecutive days at dose currently recommended in other countries (10 gr/m^2 on day -4, day -3 and day -2) before transplantation.
Intravenous administration should be performed using a safe technique to avoid extravasation.
The body surface is calculated according to the Mosteller's formula:
$S= (taille*poids/3600)^{0,5}$

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

The transplantation procedure will followed standard procedure and patients can receive a similar treatment outside the protocol. Haplo-identical transplantation are currently performed using fludarabine-alkylan based conditioning regimen and post-transplant cyclophosphamide. The trial does not guarantee any benefit for the patients. The risk is similar to an haplo-transplantation performed outside the protocol with risk of acute and chronic GVHD, risk of immune defect, mortality and disease progression. The primary aim is the efficiency of the haplo in terms of survival without disease and rejection.

3 OBJECTIVES

3.1 Primary objective

To assess the disease-free survival and without rejection at 12 months after haplo-identical transplantation.

3.2 Secondary objectives

To assess
-incidence of acute GVHD grade 2/4 at 100 days
-incidence of acute GVHD grade 3/4 at 100 days
-engraftment at 100 days
-incidence of chronic GVHD at 12 months
-non-relapse mortality at 12 months
-overall survival at 12 months
-relapse/progression incidence at 12 months
-rejection incidence at 12 months
-time to neutrophil engraftment at 60 days
-time to platelet engraftment at 100 days
-infection incidence at 100 days and at 12 months
-cytokine profile during transplantation
-impact of genetic alterations on outcome

3.3 Objective of any future ancillary study

Blood samples will be collected via CryoStem platform, (2 blood samples of 5 ml and 7 ml) at inclusion, (1 blood sample of 5 ml) 7+/- 1 days before HSCT (before conditioning regimen initiation), the day of transplantation and 7+/-1 days after transplantation.
Analyses will be performed on:
-genetic alteration in malignant cells
-cytokine release during conditioning regimen

The CRBs will be contacted by Cryostem for the setting up.

Biology will be done at the end of the study in Saint-Louis Hospital laboratory, Biology cellular, Professor Stéphane GIRAUDIER, 1 avenue Claude Vellefaux, 75475 Paris.

Lymphocyte phenotype (T/B/NK) will be done on day 30, 60, 100, 180, 365 (usually done in center at least on day 100 and one year).

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

The primary endpoint will be disease-free survival, without rejection 12 months after transplantation.

Relapse will be defined as reappearance of malignant cells in blood associated with a mixed or a recipient chimerism.

Rejection will be defined as a pancytopenia persisting 60 days after the transplantation (primary rejection) or cytopenia occurring after engraftment with graft lost (chimerism which becomes recipient) and no evidence for disease progression at any point during follow-up (secondary rejection).

4.2 Secondary endpoints

The secondary endpoints will be:
- incidence of acute grade 2-4 and grade 3-4 GVHD according to the modified Glucksberg classification (Przepiorka *et al*, 1995)
- incidence of chronic GVHD (limited vs extensive) at 12 months according to the revised Seattle criteria (Lee *et al*, 2003)
- neutrophil engraftment on day 60 post-transplantation, engraftment is defined as neutrophil count at 0.5G/L or higher for more than 3 consecutive days after transplantation, it should be confirmed by a donor chimerism
- platelet recovery: first day of platelet > 20G/L without transfusion the last 7 days assessed on day 100
- overall survival at 12 months
- non-relapse mortality at 12 months
- incidence of relapse/progression at 12 months
- incidence of rejection at 12 months
- infection incidence at 100 days, 12 months (annexe for infection)
- cytokine profile during transplantation (day-7 +/- 1 jour, J0 and day J7 +/- 1 jour)
-impact of genetic alterations on overall survival at 12 months and non-relapse morality at 12 months

4.3 Research methodology

4.3.1 Design of the trial

This a phase 2 one-group multicenter study.

4.3.2 Number of participating sites

This is a national multi-center study including 22 centers. Patients will be recruited in the hematology units.

4.3.3 Identification of the subjects

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

5 PROCEDURE FOR THE TRIAL

5.1 Screening visit

The screening visit takes place before D-90 and D-14 before transplant. The investigator checks the eligibility criteria and proposes the study to the patient. Information about the protocol is delivered by the transplant physician in charge of the patient. The diagnosis of myelofibrosis is checked and confirmed (a marrow biopsy should have been done at least once at any moment before inclusion).

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

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
the subject participating in the trial;	the investigator (state the specialist field)	Screening visit	At the baseline visit

5.2 Baseline visit

The baseline visit takes place 30 to 14 days before transplantation. At this visit, the consent of the patient will be collected. A Patient Information Sheet and consent form are given to the patient by the investigator; the original is conserved by the investigator and the third copy for the sponsor.

· Physical examination

- Reports of patient and disease history (cf Annexe) (Sorror *et al*, 2005)
- ECOG assessment (cf Annexe) (Oken *et al*, 1982)
- Sorror score of comorbidities (cf Annexe) (Mesa *et al*, 2013)
- Complete physical examination with evaluation of spleen size
-Electrocardiogram
- General symptoms associated with MF: MF-SAF form (cf Annexe)
- Evaluation of the cardiovascular risk factors (dyslipidemia, HTA, obesity, smoking).

- Radiological examinations

- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)“
- Liver ultrasound and doppler echography (baseline values)
- Total body scan
- Echocardiogram with evaluation of left ventricular ejection

· Biological test

- Complete Blood count
- Prothrombin time (PT), Partial thromboplastin time (PTT)
- ABO and Rh typing Blood cell
-Chemistry panel (serum electrolytes with creatinine, urea, calcium, glucose, uric acid, phosphate, CRP, proBNP, LDL, HDL, triglyceride, total cholesterol)
- Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubin)
- Circulating protein electrophoresis
- Pregnancy test (for women of childbearing age)
- HLA compatibility check between recipient and donor
- Search of anti-HLA antibodies with LUMINEX technology (DSA)
- Chimerism markers’ identification
- Blood karyotype (if not done previously)
- Blood collection

· Infectious assessment

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

5.3 Follow-up visits

Patients will be examined as usually by standard procedure. All the visits will be done outside the protocol.

Patients **will be monitored daily** during the hospitalization for possible complications related to the procedure or acute GvHD. The **daily monitoring** includes:

- Physical examination of the patient and safety assessment by collection of all adverse events/serious adverse events likely to occur as well as all actions taken because of these AEs. These AEs will be grading according to the CTC-AE scale.
- Complete Blood count, chemistry assessment with kidney and liver test will be performed
- Aspergillus antigen, toxoplasmosis PCR according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 will be performed weekly (or according to clinical context)
- Grading of acute GvHD will be performed weekly during hospitalization and at each visit until J120
- During conditioning regimen, **tumor lysis syndrome (TLS)** will be prevented by hyperhydration (at least 1.5L/m2) and allopurinol. In case the patient has previous renal failure, or high uricemia or high white blood counts, rasburicase will be done. During conditioning regimen, biological TLS should be monitored 1 or 2 times per 24 hours.

- **Cardiologic monitoring:** Prevention of cardiac failure will include systematic furosemide 40 mg per day during hyper-hydration, proBNP will be performed daily and ECG +

echocardiogram will be performed in cases there is a doubt on cardiac failure. Electrocardiogram will be checked before the infusion of cyclophosphamide and repeated in association to a dosage of troponin according to clinical symptoms and proBNP on a daily basis for 3 consecutive days after the administration of cyclophosphamide and repeated after if any doubt. Weight measure will be done daily during hyper-hydration or in case of overload suspicion. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide (JACIE procedure).

- Blood collection between D-7+/-1 , D0, D+7+/-1 and at inclusion (CRYOSTEM)

Patients will be assessed **at M1, M2, M3, M6, M12** as following:

- Clinical examination, blood cell count, chemistry panel with creatinine and liver test will be performed at each visit (routine follow-up).
- Chimerism evaluation at M1, M2, M3, M6, M12 (no need to repeat chimerism when 100% donor except haematological change)
- Weekly aspergillus antigen, toxoplasmosis PCR according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 : at M1, M2, M3 and until context after
- **Cardiologic monitoring**: For all patients, a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M3 and M12.
- Safety assessment by collection of all adverse events/serious adverse events at each visit

5.4 End of study visit

Patients will be followed for 24 months after transplantation in the protocol and will be followed outside the protocol after this date. The end of study visit will be at 24 months. After the end of the trial, patients will be followed according to the center policy and routine monitoring.

Patients will be followed 24 months after transplantation to analyze the occurrence of GVHD and the survival or relapse status

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

The research will be conducted during a total of **60 months:**
-**36 months to recruit** the patients which is supported by the current number of transplantation for myelofibrosis in France (100 patients per year; of them 20% received an HLA mismatched and some of them are not transplanted because of the absence of haplo trial)

-12 months of follow-up to analyze the primary endpoint which is at 12 months post transplantation

- **12 months of follow-up** after transplantation to analyze the occurrence of GVHD and the survival or relapse status

Maximum period between screening and enrolment	3 months
Length of Inclusion period	36 months
Duration of participation for each subject, of which:	
• Follow-up period:	24 months post transplantation
Total study duration:	60 months

5.6 Table or diagram summarising the chronology of the study

	Before treatment		During treatment		Follow-up						
Study procedure	Screening D-90 & D-14	Baseline visit (D-30 & D-14) **									
			conditioning regimen (-6)	Day 0= Graft	daily monitoring*	M1	M2	M3	M6	M12	M24
Information	x	x									
Inclusion, exclusion criteria checked	x										
Signature of the consent form		x									
beta-HCG test (before start treatment)		x									
Physical examination, past medical history [a]		x			x	x	x	x	x	x	
Blood test, virology test [c]		x									
Other biological test[d]		x	x	x	x	x	x	x	x	x	
Cardiac echography		x						x			
Total body scan		x						x			
Other Radiological examination[b]		x									
Tumor Lysis syndrome[#]			x								
Infectious assessment[e]		x			x	x	x	x			
Cardiologic monitoring*			x	x	x	x	x	x	x	x	
GVHD Assessment[$]					x	x	x	x	x		x
Chimerism evaluation***						x	x	x	x	x	x
Adverse and serious adverse event			x	x	x	x	x	x	x	x	x
Lymphocyte phenotype						x	x	x	x	x	
Biocollection : plasma (CRYOSTEM)****		x	x	x	x						

[a] *Reports of patient and disease history, ECOG assessment, HTIC- score, Sorror score of comorbidities, Complete physical examination with evaluation of spleen size, Electrocardiogram, Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking), spleen size*

[b] *Pulmonary function tests, Liver ultrasound and doppler*

[c] *Blood karyotype, Prothrombin time (PT), Partial thromboplastin time (PTT) ,ABO and Rh typing Blood cell, Chemistry panel, Circulating protein electrophoresis, HLA compatibility, Search of anti-HLA antibodies with LUMINEX technology (DSA), Chimerism markers' identification, blood karyotype (if not done previously), Serology for hepatitis B and C, HIV (2 Elisa tests), HTLV-1 and 2, toxoplasmosis (IgG and M), TPHA and VDRL, HSV (IgG and M),*

[d] *Complete Blood count including % blast, Liver function tests (transaminases, alkaline phosphatase, gamma-GT, PAL and bilirubin),Kidney function tests (creatininemia, LDH, uric acid, calcemia, phosphoremia)*

[e] *Aspergillus antigen, EBV (IgG and M), CMV (IgG and M), adenovirus, HHV-6 (performed weekly during the first months then at M1,M2 and M3 and according to clinical context after)*

[$] *performed weekly during hospitalization and at each visit until J120*

[#] *monitored 1 or 2 times per 24 hours during conditioning regimen*

* *weight measure will be done once a day during the first 3 weeks. New echography will be immediately done if necessary. Physical cardiac exam, electrocardiogram and cardiac echography will be done at M3 and M12*

***can be day -6 or another day before transplantation but should be before conditioning regimen*

****As soon as the chimerism is 100% donor in blood and hematological data are stable, it is not necessary to redone it*

***** 2 additional tubes (1 EDTA 5ml and 1 sec 7 ml) at inclusion , 1 tube sec 7 ml at D-7+/-1, D=0 and D+7+/-1 (overall 4 additional blood samples of 5 ml and 1 blood sample of 7ml)*

5.7 Distinction between standard care and research

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

Procedures and treatments to be provided during the study	**Procedures and treatments associated with <u>standard care</u>**	**Procedures and treatments added for the <u>study</u>**
Treatments		Allogenic transplantation using treosulfan and fludarabine and thiotepa in conditioning regimen
Consultations	standard	
Blood samples		2 additional tubes (1 EDTA 5 ml and 1 sec 7 ml) at inclusion , 1 tube sec 7 ml at D-7+/-1, D=0 and D+7+/-1 (overall 4 additional blood samples of 5 ml and 1 blood sample of 7 ml) 1 additional tube of 7 ml at day 30, 60 and 180
Imaging, etc.	standard	
….		

5.8 Biological samples

The samples that are taken during the trial (blood and serum) will be stored in a biological sample bank.

During the trial, the sample(s) will be stored at the local Centre de Ressources Biologiques (CRB) affiliated to CRYOSTEM in each center (see addendum) under the supervision of .each PI for a duration of 10 years.

At the end of the trial, the samples may be used for further analysis not described in the initial protocol but which may be useful for our investigation of the condition (specify)/in light of developments in scientific knowledge, provided the subject is informed and gives consent, as stated in the information sheet/consent form.

If the samples are kept at the end of the trial, the sample bank will be declared to the relevant minister (Article L. 1243-3 CSP).

Type of sample	**Quantity**	**Storage location**	**Manager of the sample bank**	**Purpose of the sample bank**	**Storage period**	**Outcome (destruction, etc.)**
Blood	4 ml x 4 7ml x1	CRB	cryostem	cryostem	36 months	Destruction after 10 years

5.9 Termination and exit rules

5.9.1 Criteria and procedures for prematurely terminating the study treatment

5.9.2 Different situations

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

The investigator must:

- Document the reason(s)
- Collect all endpoints at the moment the subject exits from the study, if the subject agrees
- Schedule further follow-up visits, especially in case of a serious adverse event.

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

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

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

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

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

5.9.1 Monitoring subjects after the premature termination of treatment

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 3 months following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse reaction will be monitored until it is resolved.

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

5.9.2 Full or partial cancellation of the study

AH-HP (the sponsor) or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Monitoring Committee in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) requiring a reassessment of the benefit-risk ratio for the trial.

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

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

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- ✓ Patients aged from 18 to 70 years
- ✓ Primary myelofibrosis or myelofibrosis secondary to essential thrombocythemia or polycythemia Vera proven by marrow biopsy
- ✓ Performance status according to ECOG at 0, 1 or 2
- ✓ The myelofibrosis should combine at least 2 of the following criteria:
  - ✓ constitutional symptoms: weight loss > 10% in one year, fever (without infection), recurrent muscle, bone or join pains, extreme fatigue
  - ✓ anemia with hemoglobin < 10 gr/dL or red blood cell transfusion
  - ✓ thrombocytopenia < 100 G/L
  - ✓ peripheral blast count > 1% at least found 2 times
  - ✓ white blood cell count > 25 G/L (before a cytoreductive treatment)
  - ✓ Karyotype: +8, -7/7q-, i(17q), -5, 5q-, 12p-, inv(3), 11q23
- ✓ With health insurance coverage
- ✓ Having signed a written informed consent
- ✓ Women agreed to take nomegestrol acetate as contraception during and up to 6 months after treatment by treosulfan
- ✓ Men agreed not to conceive child during and up to 6 months after treatment by treosulfan

6.2 Exclusion criteria

- ✓ Myelofibrosis transformed into acute leukemia
- ✓ Poor performance status with ECOG 3 or more
- ✓ Cardiac failure with EF < or = 50% currently or in the past (even if corrected after treatment)
- ✓ Renal failure with creatininemia > 120 µmol/L or clearance < 50 ml/min
- ✓ Respiratory function altered with vital capacity < 70% or forced expired volume < 70%
- ✓ Biological significant liver abnormalities; ASAT or ALAT> 2 x normal range, bilirubin > 1.5 x normal range
- ✓ HLA matched donor available
- ✓ Tutorship or curatorship
- ✓ Unwilling or unable to comply with the protocol
- ✓ Pregnant woman or breastfeeding
- ✓ Contraindications to treosulfan
  - Hypersensitivity to the active substance
  - Active non-controlled infectious disease
  - Fanconi anaemia and other DNA breakage repair disorders
  - Administration of live vaccine
- ✓ Contraindications or any circumstance that precludes the use of the drugs involved in the protocol (especially Thiotepa and Fludarabine)

6.3 Recruitment methods

	Number of subjects
Total number of subjects to be included	28
Number of sites	22
Enrolment period (months)	36
Number of subjects/site	1.3
Number of subjects/site/month	**0.03**

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Donor Selection

An haplo-identical donor is a familial donor sharing an inherited HLA haplotype with the recipient.

All donors should be assessed by a specific physician (different from the physician in charge of the patients)
Contraindication for a donor:
- DSA > 5000 MFI
- Age ≥ 70 years or < 18 years

Following future legal authorization, 16 or 17 years donor can be selected if there is no other alternative donor (not authorized the 22/04/2021 yet)

The selection of the donor will followed standard of case as defined by JACIE or FACT

Criteria for donor selection (in case there are several haplo-identical donors) and by priority order:
-donor HLA specific antibodies in the patients should be < 5000 (mean fluorescence intensity)
-CMV- for a patient who is CMV- / CMV+ for a patient who is CMV+
-no major ABO incompatibility
-the youngest donor
-donor weight should be close to recipient weight

7.2 Transplants modalities

Before to start treatments, a βHCG test will be done. All patients will received similar conditioning regimen and GVHD prophylaxis.

7.2.1 Conditioning regimen

Conditioning regimen will be as follow:

	-6	-5	-4	-3	-2	-1
Treosuflan IV			10 gr/m^2	10 gr/m^2	10 gr/m^2	
Fludarabine IV		30 mg/m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2
Thiotepa IV	5 mg/kg*					

Chemotherapy will be reconstituted by trained personnel in a specific area according to good pharmacy practice.

CYP2B6 and CYP3A4 inhibitors including Azole (anti-fungal therapy) and P450 cytochrome inducers will be stopped at least 24 hours before starting conditioning regimen.

Conditioning regimen will be administered via central venous catheter only.

Treosulfan will be administered IV 2 hours and before fludarabine IV injection
Fludarabine will be administered IV 30 minutes and after treosulfan perfusion
Thiotepa will be administered IV 2 hours
*In overweight patients (>120% PCI), thiotepa will be adjusted according to PCIA40 as follow:
PCI man = 50 + 0;91 x (height in cm – 152)
PCI woman = 45 + 0,91 x (height in cm – 152)
PCIA40 = PCI + 0,40 x (weight in kg – PCI)

During conditioning regimen, **tumor lysis syndrome prophylaxis should be applied** with close monitoring (at least each day from D-6 until D+6), allopurinol 300 mg/jour, hyperhydration (at least 2 L/m^2) + furosemide 40 mg per day and surveillance of diuresis / 6 hours with additional furosemide in cases of diuresis delay

7.2.2 Type of stem cell source

The stem cell source will be preferentially peripheral blood stem cells (PBSC), alternatively it will be marrow (BM)
When stem cells are infused fresh:
-Number of CD34 cells required is 4 or more 10exp6/kg with PBSC.
-Number of nucleated cells required is 3 or more 10exp8/kg with marrow.
In cases for different reasons independent from the protocol, the stem cells should be cryopreserved before thawing and infusion to the patient:
-Number of CD34 cells required is 6 or more 10exp6/kg with PBSC.
-Number of nucleated cells required is 4 or more 10exp8/kg with marrow.
If possible, don't cryopreserved the marrow, collect PBSC.

7.2.2 GVHD prophylaxis

Prophylaxis of GVHD will be as follow according to recommendations of standard care.

	0	Day 1	Day 2	Day 3	Day 4	Day 5
Cyclosporine IV*	3mg/kg	3mg/kg	3mg/kg	3mg/kg	3mg/kg	3mg/kg
Mycophenolate mofetil**		30mg/kg	30mg/kg	30mg/kg	30mg/kg	30mg/kg
Cyclophosphamide IV				50 mg/kg		50 mg/kg

*adjusted to dosage, target between 200 and 400 ng/mL until day 180 if no GVHD
**mycophenolate can be administrated in 2 or 3 take per day for a total dose at 30mg/kg (15mg/kg x 2 day or 10mg/kg x 3 per day per multiple of 250 mg) preferably IV at the beginning until day 30).

Cyclosporine will be dosed on day 2 and adapted at least once a week to target level between 200 and 400 ng/L. In case of renal failure attributable to cyclosporine, dose will be decreased according to good practice.
No dosage are needed for mycophenolate mofetil and cyclophosphamide.
Cyclophosphamide will be prepared according to good pharmacy practice and will be administered IV 2 hours on central venous catheter associated with Mesna 50 to 100% of cyclosphosphamide dose. In patients with overweight (PCI<120%), the dose will be adapted according to PCIA24 as follow:PCI man = 50 + 0;91 x (height in cm – 152)
PCI woman = 45 + 0,91 x (height in cm – 152)
PCIA25 = PCI + 0,25 x (weight in kg – PCI)

Hyperhydratation will be performed during cyclophosphamide administration (1.5L/m^2) and diuresis will be monitored every 3 hours with systematical furosemide (40 mg per day on day 3 and day 5).

7.2.3 Ruxolitinib management

If the patient is treated by ruxolitinib before the transplantation, it will be continued until the day of transplantation (stopping that day).

7.2.4 Infectious prophylaxis

All patients should receive prophylaxis against herpes simplex virus (oral valacyclovir 1gr/day or IV acyclovir 15mg/kg/day) and invasive fungal infection (left to physician discretion).
After neutrophil count > 0.5 G/L, patients should receive pneumocystis/toxoplasmosis prophylaxis. In case aplasia is 30 days or longer, this prophylaxis can be started on day 30 after transplantation.
Patients CMV seropositive will receive letermovir as CMV prophylaxis from day – 1.

7.2.5 Splenectomy

There is no specific recommendation regarding splenectomy before transplantation but splenectomy can be justified in patients with huge spleen estimated at several kilograms in scan or in patients with spleen complications (hemorrhage, infarct, pain). It is usually not necessary in patients with spleen size estimated at < 20 cm for the largest measure because it decreases spontaneously after HSCT.

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

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

7.3.1 Authorized treatments

Anti-infectious treatments (antibiotics, antivirals, antifungals), transfusions, growth factors according to usual practice of each centres are authorized.
See above for association contraindicated during conditioning regimen, all medications can be started again after conditioning regimen except ruxolitinib which is stopped on day 0.

7.3.2 Treatments forbidden

Yellow fever vaccine and alive vaccines are contraindicated.

7.3.3 Treatments not recommended

- For cyclophosphamide :
  - Attenuated vaccine (contraindication in the setting of transplantation for yellow fever vaccine)
  - Phenytoin
  - Pentostatine

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

- For Thiotepa :
  - Phenytoin , Fosphénytoïne
  - CYP2B6 and CYP3A4 inhibitors including Azole (anti-fungal therapy) and P450 cytochrome
  - Attenuated vaccine (contraindication in the setting of transplantation for yellow fever vaccine)

- Treosulfan : - no interaction with treosulfan has been reported with intensive chemotherapy

7.4 Management of relapse

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

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

8.1.1 Disease free survival

Disease free survival is defined as the time from graft until the occurrence of following events: refractory disease, relapse, death from any cause whichever comes first right.

Relapse will be defined as reappearance of malignant cells in blood associated with a mixed or a recipient chimerism.

Rejection will be defined as a pancytopenia persisting 60 days after the transplantation (primary rejection) or cytopenia occurring after engraftment with graft lost (chimerism which becomes recipient) and no evidence for disease progression (secondary rejection).

8.1.2 Acute GvHD

Acute GvHD is defined according to the modified Glucksberg classification (Przepiorka *et al*, 1995), detailed in annexe. Treatment of grade 2 acute GVHD will consist in high dose of methylprednisolone (2mg/kg in cases of grade II). Grade 1 acute skin GVHD can be treated by topic (diprosone®) or high dose of methylprednisolone if itching, pain or inflammatory skin. In cases of refractoriness to steroids (progression after 3 days, stable after 7 days), a second line therapy will be discussed according to the discretion of physician and starting with a medication approved in the country if any, extra-corporeal photophoresis or any immunosuppressive therapy under investigation or with published data in the treatment of acute GVHD.

8.1.3 Chronic GvHD

Chronic GvHD is defined according to according to the revised Seattle criteria (Lee *et al*, 2003), detailed in annexe. Chronic GVHD refractory to steroids (no response after 4 weeks) will be treated by a medication approved in the country if any, extra-corporeal photophoresis or any immunosuppressive therapy under investigation or with published data in the treatment of chronic GVHD.

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

The parameters for assessing efficacy were collected according to the schedule in table paragraph 5.5

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific Committee

Members of the committee: Marie Robin, Sylvie Chevret and for DRCI : Project manager and Clinical Research Assistant.

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

9.2 Data safety monitoring board (DSMB)

See “Safety section” 10.2.4 page 40.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Safety endpoints

The safety assessment shall be done by collecting all adverse events that occur during the research. All adverse events (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale (v4.03). Acute-GvHD shall be graded according to modified Glucksberg classification**.**

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

10.2 Recording and reporting adverse events

10.2.1 Definitions

According to Article R1123-57 of the French Public Health Code:

- **Adverse event**

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

- **Adverse reaction**

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

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

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

- **Serious adverse event or reaction**

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

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

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

- **Emerging safety issue**

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

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,

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

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

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

10.2.2 The role of the investigator

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

The investigator must **assess the severity** of the adverse events by using:
- CTA-AE Toxicity Grading Scale, v5.0
- Modified Glucksberg classification for acute GvHD

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product or interventions/procedures added by the study.

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

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

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

Table: WHO-UMC causality categories (excerpt)

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

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

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

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

As per article R.1123-57 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring a notification without delay.The sponsor shall report to the ANSM all serious adverse reactions and serious incidents occurring in France and outside the national territory in the research it conducts, without delay from the day on which it becomes aware of them.

A serious adverse event is any untoward medical occurrence that:

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

10.2.2.2 Specific features of the protocol

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

- Adverse events deemed "medically significant":
  - Grade 3 or 4 acute GVHD
  - Graft rejection
  - Platelet < 20G/L after day 100 post HSCT (in patients without graft rejection or grade 3-4 GVHD)
  - Haemoglobin level < 7gr/dL after day 180 post HSCT (in patients without graft rejection or grade 3-4 GVHD)
  - Grade 3/4 toxicity (except haematological toxicity which is expected for all patients)
  - Tumor lysis syndrome
  - Acute cardiac failure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).The sponsor shall report to the ANSM all serious adverse reactions and serious incidents occurring in France and outside the national territory in the research it conducts, without delay from the day on which it becomes aware of them.

- Adverse events of special interest
  The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).The sponsor shall report to the ANSM all serious adverse reactions and serious incidents occurring in France and outside the national territory in the research it conducts, without delay from the day on which it becomes aware of them.

- ***In utero*** exposure

The investigator must notify the sponsor **without delay on the day the investigator becomes aware** of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.
The sponsor shall report to the ANSM all serious adverse reactions and serious incidents occurring in France and outside the national territory in the research it conducts, without delay from the day on which it becomes aware of them.

- Exposure **while breastfeeding**
  Exposure while breastfeeding occurs if an infant or child may have been exposed to a medicinal product via the breast milk of a mother being treated with an investigational medicinal product.

  Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day when the investigator becomes aware of the exposure while breastfeeding.
  The sponsor shall report to the ANSM all serious adverse reactions and serious incidents occurring in France and outside the national territory in the research it conducts, without delay from the day on which it becomes aware of them.

*10.2.2.2.2 **Serious adverse events that do not require the investigator to notify the sponsor***

These serious adverse events are only recorded in the case report form. A CRF extraction of these serious adverse events will be realized every 3 months by the clinical research unit and sent to the Safety Department by email (expertisecsi.drc@aphp.fr) .

- *Normal and natural course of the condition*:
  - Scheduled inpatient hospitalization for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]
  - Inpatient hospitalization for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
  - Emergency inpatient hospitalization upon enrollment or prolongation of hospitalization upon enrollment for monitoring the condition under investigation
  - Worsening of the condition under investigation
  - In case of disturbance of biological values corresponding to an adverse event of grade ≤ 3 and no other symptoms (fever, etc.) associated with this adverse event, this event will not be notified to the sponsor as a serious adverse event but only recorded in the case report form.

All the following events which are frequent after transplantation have not to be notified

Expected Adverse events during the trial possibly related to the graft procedure
Most common post-transplant symptoms in the acute phase :

- digestive disorders with diarrhea, nausea, vomiting, abdominal pain, lack of appetite, modified taste
-inflammation of the mouth (mouth ulcers) or throat (like angina)
-rows, itching, burns
-jaundice
-asthenia or feeling dizzy or difficulty concentrating
-sleeping troubles
- bone, joint or muscle pain

-headache
-dyspnea
-cough
-Hair loss
- leg edema or swelling of the face or other part of the body
-fever
-bladder pain or pain while urinating
-bleeding : mouth, nose, stool, urine, vomiting
- cytopenia post-chemotherapy
neutropenia that resolved within 60 days after HSCT
-thrombocytopenia that resolved within 100 days after HSCT
-red blood cells transfusion that resolved within 180 days after HSCT

-Grade I-II acute GvHD

Most common post-transplant symptoms in the later phase :

the complications of the acute phase can also occur later but more rarely
-relapse of myelofibrosis
-brittle tongues
- dry eyes and mouth
- genital dryness
-hypofertility and infertility
-early menopause
-problem of functioning of the thyroid gland
-hyperpilosity
-loss of joint flexibility
-thickening of the skin and / or pigmentation (skin becoming darker in places) or depigmentation of the skin (skin becoming whiter in places)
-muscle loss and asthenia during exercise
-fragility of bone with possibility of fracture (osteoporosis) and joint pain related or not to osteonecrosis (problem of intraosseous vascular malfunction)

-chronic GvHD

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

The investigator notifies the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant signs the consent form
- throughout the whole follow-up period required for the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

10.2.2.4 Procedures and deadlines for notifying the sponsor

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

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

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

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

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

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

For trials which use e-CRF

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

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

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

10.2.3 Role of the sponsor

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

10.2.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all adverse events reported,
- the **causal relationship** between these events and each investigational medicinal product and/or study procedures and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics is considered unexpected.
The sponsor, represented by its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product:

☐ refer to the SmPC for Treosulfan enclosed in appendix 3 (reference http://base-données-publique.medicaments.gouv.fr).

❖ For serious adverse events likely to be related to the additional medicinal products:

☐ refer to the SmPC for Fludarabine, Thiotepa, Cyclophosphamide, Mycophenolate mofetil and Cyclosporine enclosed in appendix 4 (reference http://base-données-publique.medicaments.gouv.fr).

For serious adverse events likely to be related to

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:
- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.

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

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the trial subjects.
Specific case of serious adverse events of special interest.
The sponsor may be required to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as for SUSARs.

10.2.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, or which could be sufficient to consider changes to the use of the investigational medicinal product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe which measures have been taken.

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

10.2.3.3 Annual safety report

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

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

10.2.4 Data Safety Monitoring Board (DSMB)

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

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The members of the DSMB are:
Raphael Porcher (Hôtel Dieu Hospital, Paris, France)
Hugues De Lavallade (King's College Hospital, London, UK)
Philippe Lewalle (Jules Bordet Institute, Bruxelles, Belgium)

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.
The DSMB will take place at least every year or more often if DMSB considers, during the meeting prior to the start of the study, that a higher frequency is necessary. Moreover, members of the DSMB will receive a synthesis of SAEs every 4 months. They would be able to request at any moment a DSMB meeting if needed.

11 DATA MANAGEMENT

Data collection

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

11.2 Right to access source data and documents

11.2.1.1 Access to data

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2.1.2 Source documents

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

11.2.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

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

The management and processing of the data will be done by the Service de Biostatistique et Information Médicale (SBIM), hôpital saint Louis, Paris (Pr. Sylvie Chevret). Data entry
Data will be entered electronically via a web browser.

11.3.2 Data entry

e-CRF: Data will be entered electronically via a web browser.

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

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

11.3.4 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the trial.

This indexed archiving includes, in particular:

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

.

11.4 Ownership of the data

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

12 STATISTICAL ASPECTS

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

The analysis will be based on the intent-to-treat basis, that is, including all patients whatever they were administered the treatment under study or not. Only patient consent withdrawals with positive report of not using their data, if any, will be excluded.
Baseline summary statistics, namely percentages or median [interquartile range, IQR], will be performed..
The right censored endpoint will be estimated using nonparametric methods. Kaplan Meier curves and cumulative incidence curves will be considered in case of non informative or informative censoring based on the log-rank test or the Gray test, respectively. Adjustment on potential confounders will used the Cox proportional hazards models. Model assumptions will be checked using a test for proportional hazards and spline smoothing of residuals for the log-linearity assumption.
A sensitivity analysis will be performed in patients who will actually receive the graft. Statistical analyses will be performed on SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.

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

The hypothesis is that survival without event (disease or rejection) is more than 55% one year after transplantation instead of 30%.
A two-side, one-sample logrank test calculated from a sample of **28 subjects**, 90% power at a 0.050 significance level to detect a proportion of survival of 55% in the new group when the proportion surviving

in the historic control is 25%. These proportions surviving are for a period of 1 year. Subjects are accrued for a period of 24 months. Follow-up continues for a period of 24 months after the last subject is added.

12.3 In the case of a comparative randomised study, the calculation is based on a hypothesis of a difference between the two groups for the primary endpoint, and is a function of the accepted ALPHA and BETA risks, of the uni-or bilateral formulation and of the variance (in the case of a quantitative variable).

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

12.5 Anticipated level of statistical significance

The type I error is fixed at α=0.05.

12.6 Statistical criteria for termination of the study.

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

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

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

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

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

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

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

- the research subjects are safe, protected and their rights are being met

• the data being recorded is accurate, complete and consistent with the source documents
• the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

13.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan.

13.1.2.Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study.Therefore the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: D level.

13.2 Quality control

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

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

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

13.3 Case Report Form

Electronic CRF:

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.

Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

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

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

13.5 Audits/inspections

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

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

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.6 Principal Investigator's declaration of responsibility

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

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

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

13.7 Pharmacist's declaration of responsibility

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

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

The person’s free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator after a sufficient time to think during inclusion visit and before randomization.

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

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

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

During his participation to FIBRAPLO study, the patient may not participate in other interventional research protocol relating to a medicinal product for human use without first speaking to the doctor in charge of this trial.

There is no exclusion period after the research

14.3 Legal obligations

14.4 The sponsor's role

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

14.5 Request for approval from the Institutional Review Board

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

14.6 Request for approval from the ANSM

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

14.7 Declaration of compliance with the MR 001 "Reference Method"

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

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

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

14.8 Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the

amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

14.9 Final study report

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

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

The research was funded by 2 industrial grants.

15.2 Insurance

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

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

16 PUBLICATION

16.1 Mention of AP-HP affiliation for projects sponsored or managed by AP-HP

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

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

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

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

17 BIBLIOGRAPHY

Ballen, K.K., Shrestha, S., Sobocinski, K.A., Zhang, M.-J., Bashey, A., Bolwell, B.J., Cervantes, F., Devine, S.M., Gale, R.P., Gupta, V., Hahn, T.E., Hogan, W.J., Kröger, N., Litzow, M.R., Marks, D.I., Maziarz, R.T., McCarthy, P.L., Schiller, G., Schouten, H.C., Roy, V., et al (2010) Outcome of transplantation for myelofibrosis. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **16,** 358–367.

Baronciani, D., Depau, C., Targhetta, C., Derudas, D., Culurgioni, F., Tandurella, I., Latte, G., Palmas, A. & Angelucci, E. (2016) Treosulfan-fludarabine-thiotepa conditioning before allogeneic haemopoietic stem cell transplantation for patients with advanced lympho-proliferative disease. A single centre study. *Hematological Oncology*, **34,** 17–21.

Barraco, D., Mudireddy, M., Shah, S., Hanson, C.A., Ketterling, R.P., Gangat, N., Pardanani, A. & Tefferi, A. (2017) Liver function test abnormalities and their clinical relevance in primary myelofibrosis. *Blood Cancer Journal*, **7,** e557.

Bashey, A., Zhang, X., Sizemore, C.A., Manion, K., Brown, S., Holland, H.K., Morris, L.E. & Solomon, S.R. (2013) T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol*, **31,** 1310–6.

Beelen, D.W., Trenschel, R., Stelljes, M., Groth, C., Masszi, T., Reményi, P., Wagner-Drouet, E.-M., Hauptrock, B., Dreger, P., Luft, T., Bethge, W., Vogel, W., Ciceri, F., Peccatori, J., Stölzel, F., Schetelig, J., Junghanß, C., Grosse-Thie, C., Michallet, M., Labussiere-Wallet, H., et al (2019) Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *The Lancet. Haematology*.

Beelen, D.W., Trenschel, R., Stelljes, M., Masszi, T., Reményi, P., Wagner-Drouet, E.-M.M., Dreger, P., Bethge, W., Ciceri, F., Stoelzel, F., Junghanss, C., Michallet, M. & Markiewicz, M. (2017) Final Results of a Prospective Randomized Multicenter Phase III Trial Comparing Treosulfan/Fludarabine to Reduced Intensity Conditioning with Busulfan/Fludarabine Prior to Allogeneic Hematopoietic Stem Cell Transplantation in Elderly or Comorbid Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome. *Blood*, **130,** 521–521.

Brabrand, M., Hansen, K.N., Laursen, C.B., Larsen, T.S., Vestergaard, H. & Abildgaard, N. (2019) Frequency and etiology of pulmonary hypertension in patients with myeloproliferative neoplasms. *European Journal of Haematology*, **102,** 227–234.

Bradstock, K., Bilmon, I., Kwan, J., Blyth, E., Micklethwaite, K., Huang, G., Deren, S., Byth, K. & Gottlieb, D. (2015) Influence of Stem Cell Source on Outcomes of Allogeneic Reduced-Intensity Conditioning Therapy Transplants Using Haploidentical Related Donors. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **21,** 1641–1645.

Bregante, S., Dominietto, A., Ghiso, A., Raiola, A.M., Gualandi, F., Varaldo, R., Di Grazia, C., Lamparelli, T., Luchetti, S., Geroldi, S., Casarino, L., Pozzi, S., Tedone, E., Van Lint, M.T., Galaverna, F., Barosi, G. & Bacigalupo, A. (2015) Improved Outcome of Alternative Donor Transplants in Patients with Myelofibrosis: from unrelated to haploidentical family donors. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*.

Casper, J., Wolff, D., Knauf, W., Blau, I.W., Ruutu, T., Volin, L., Wandt, H., Schäfer-Eckart, K., Holowiecki, J., Giebel, S., Aschan, J., Zander, A.R., Kröger, N., Hilgendorf, I., Baumgart, J., Mylius, H.A., Pichlmeier, U. & Freund, M. (2010) Allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies after dose-escalated treosulfan/fludarabine conditioning. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **28,** 3344–3351.

Castagna, L., Crocchiolo, R., Furst, S., Bramanti, S., El Cheikh, J., Sarina, B., Granata, A., Mauro, E., Faucher, C., Mohty, B., Harbi, S., Chabannon, C., Carlo-Stella, C., Santoro, A. & Blaise, D. (2014) Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **20,** 724–729.

Choudhary, D., Sharma, S.K., Gupta, N., Kharya, G., Pavecha, P., Handoo, A., Setia, R. & Katewa, S. (2013) Treosulfan-thiotepa-fludarabine-based conditioning regimen for allogeneic transplantation in patients with thalassemia major: a single-center experience from north India. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **19,** 492–495.

Ciurea, S.O., Mulanovich, V., Saliba, R.M., Bayraktar, U.D., Jiang, Y., Bassett, R., Wang, S.A., Konopleva, M., Fernandez-Vina, M., Montes, N., Bosque, D., Chen, J., Rondon, G., Alatrash, G., Alousi, A., Bashir, Q., Korbling, M., Qazilbash, M., Parmar, S., Shpall, E., et al (2012) Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **18,** 1835–1844.

Ciurea, S.O., Zhang, M.-J., Bacigalupo, A.A., Bashey, A., Appelbaum, F.R., Aljitawi, O.S., Armand, P., Antin, J.H., Chen, J., Devine, S.M., Fowler, D.H., Luznik, L., Nakamura, R., O'Donnell, P.V., Perales, M.-A., Pingali, S.R., Porter, D.L., Riches, M.R., Ringdén, O.T.H., Rocha, V., et al (2015) Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*, **126,** 1033–1040.

Deeg, H.J., Gooley, T.A., Flowers, M.E.D., Sale, G.E., Slattery, J.T., Anasetti, C., Chauncey, T.R., Doney, K., Georges, G.E., Kiem, H.-P., Martin, P.J., Petersdorf, E.W., Radich, J., Sanders, J.E., Sandmaier, B.M., Warren, E.H., Witherspoon, R.P., Storb, R. & Appelbaum, F.R. (2003) Allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Blood*, **102,** 3912–3918.

Di Bartolomeo, P., Santarone, S., De Angelis, G., Picardi, A., Cudillo, L., Cerretti, R., Adorno, G., Angelini, S., Andreani, M., De Felice, L., Rapanotti, M.C., Sarmati, L., Bavaro, P., Papalinetti, G., Di Nicola, M., Papola, F., Montanari, M., Nagler, A. & Arcese, W. (2013) Haploidentical, unmanipulated, G-CSF-primed bone marrow transplantation for patients with high-risk hematologic malignancies. *Blood*, **121,** 849–57.

Di Stasi, A., Milton, D.R., Poon, L.M., Hamdi, A., Rondon, G., Chen, J., Pingali, S.R., Konopleva, M., Kongtim, P., Alousi, A., Qazilbash, M.H., Ahmed, S., Bashir, Q., Al-atrash, G., Oran, B., Hosing, C.M., Kebriaei, P., Popat, U., Shpall, E.J., Lee, D.A., et al (2014) Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **20,** 1975–1981.

Ditschkowski, M., Elmaagacli, A.H., Trenschel, R., Gromke, T., Steckel, N.K., Koldehoff, M. & Beelen, D.W. (2012) Dynamic International Prognostic Scoring System scores, pre-transplant therapy and

chronic graft-versus-host disease determine outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Haematologica*, **97,** 1574–1581.

Gupta, V., Kosiorek, H.E., Mead, A., Klisovic, R.B., Galvin, J.P., Berenzon, D., Yacoub, A., Viswabandya, A., Mesa, R.A., Goldberg, J., Price, L., Salama, M.E., Weinberg, R.S., Rampal, R., Farnoud, N., Dueck, A.C., Mascarenhas, J.O. & Hoffman, R. (2019) Ruxolitinib Therapy Followed by Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation for Myelofibrosis: Myeloproliferative Disorders Research Consortium 114 Study. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **25,** 256–264.

Iurlo, A., Cattaneo, D., Giunta, M., Gianelli, U., Consonni, D., Fraquelli, M., Orofino, N., Bucelli, C., Bianchi, P., Augello, C., Bosari, S., Colombo, M. & Cortelezzi, A. (2015) Transient elastography spleen stiffness measurements in primary myelofibrosis patients: a pilot study in a single centre. *British Journal of Haematology*, **170,** 890–892.

Kawamura, K., Kako, S., Mizuta, S., Ishiyama, K., Aoki, J., Yano, S., Fukuda, T., Uchida, N., Ozawa, Y., Eto, T., Iwato, K., Kanamori, H., Kahata, K., Kondo, T., Sawa, M., Ichinohe, T., Atsuta, Y. & Kanda, Y. (2017) Comparison of Conditioning with Fludarabine/Busulfan and Fludarabine/Melphalan in Allogeneic Transplantation Recipients 50 Years or Older. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **23,** 2079–2087.

Kröger, N., Holler, E., Kobbe, G., Bornhäuser, M., Schwerdtfeger, R., Baurmann, H., Nagler, A., Bethge, W., Stelljes, M., Uharek, L., Wandt, H., Burchert, A., Corradini, P., Schubert, J., Kaufmann, M., Dreger, P., Wulf, G.G., Einsele, H., Zabelina, T., Kvasnicka, H.M., et al (2009) Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*, **114,** 5264–5270.

Kröger, N.M., Deeg, J.H., Olavarria, E., Niederwieser, D., Bacigalupo, A., Barbui, T., Rambaldi, A., Mesa, R., Tefferi, A., Griesshammer, M., Gupta, V., Harrison, C., Alchalby, H., Vannucchi, A.M., Cervantes, F., Robin, M., Ditschkowski, M., Fauble, V., McLornan, D., Ballen, K., et al (2015) Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. *Leukemia* Available at: http://www.nature.com/doifinder/10.1038/leu.2015.233 [Accessed September 18, 2015].

Lee, S.J., Vogelsang, G. & Flowers, M.E.D. (2003) Chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **9,** 215–233.

Luznik, L., Bolaños-Meade, J., Zahurak, M., Chen, A.R., Smith, B.D., Brodsky, R., Huff, C.A., Borrello, I., Matsui, W., Powell, J.D., Kasamon, Y., Goodman, S.N., Hess, A., Levitsky, H.I., Ambinder, R.F., Jones, R.J. & Fuchs, E.J. (2010) High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. *Blood*, **115,** 3224–3230.

Luznik, L., O'Donnell, P.V. & Fuchs, E.J. (2012) Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. *Seminars in Oncology*, **39,** 683–693.

Luznik, L., O'Donnell, P.V., Symons, H.J., Chen, A.R., Leffell, M.S., Zahurak, M., Gooley, T.A., Piantadosi, S., Kaup, M., Ambinder, R.F., Huff, C.A., Matsui, W., Bolanos-Meade, J., Borrello, I., Powell, J.D., Harrington, E., Warnock, S., Flowers, M., Brodsky, R.A., Sandmaier, B.M., et al (2008) HLA-haploidentical bone marrow transplantation for hematologic malignancies using

nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*, **14,** 641–50.

Mesa, R.A., Gotlib, J., Gupta, V., Catalano, J.V., Deininger, M.W., Shields, A.L., Miller, C.B., Silver, R.T., Talpaz, M., Winton, E.F., Harvey, J.H., Hare, T., Erickson-Viitanen, S., Sun, W., Sandor, V., Levy, R.S., Kantarjian, H.M. & Verstovsek, S. (2013) Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **31,** 1285–1292.

Nemecek, E.R., Guthrie, K.A., Sorror, M.L., Wood, B.L., Doney, K.C., Hilger, R.A., Scott, B.L., Kovacsovics, T.J., Maziarz, R.T., Woolfrey, A.E., Bedalov, A., Sanders, J.E., Pagel, J.M., Sickle, E.J., Witherspoon, R., Flowers, M.E., Appelbaum, F.R. & Deeg, H.J. (2011) Conditioning with treosulfan and fludarabine followed by allogeneic hematopoietic cell transplantation for high-risk hematologic malignancies. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **17,** 341–350.

O'Donnell, P.V., Eapen, M., Horowitz, M.M., Logan, B.R., DiGilio, A., Brunstein, C., Fuchs, E.J., Flowers, M.E.D., Salit, R., Raj, K., Pagliuca, A., Bradstock, K., Granata, A., Castagna, L., Furst, S. & Blaise, D. (2016) Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: a matched-pair analysis. *Bone Marrow Transplantation*, **51,** 1599–1601.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T. & Carbone, P.P. (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*, **5,** 649–655.

Passamonti, F., Cervantes, F., Vannucchi, A.M., Morra, E., Rumi, E., Cazzola, M. & Tefferi, A. (2010) Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. *Blood*, **116,** 2857–2858.

Patriarca, F., Bacigalupo, A., Sperotto, A., Isola, M., Soldano, F., Bruno, B., van Lint, M.T., Iori, A.P., Santarone, S., Porretto, F., Pioltelli, P., Visani, G., Iacopino, P., Fanin, R., Bosi, A. & GITMO (2008) Allogeneic hematopoietic stem cell transplantation in myelofibrosis: the 20-year experience of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Haematologica*, **93,** 1514–1522.

Przepiorka, D., Weisdorf, D., Martin, P., Klingemann, H.G., Beatty, P., Hows, J. & Thomas, E.D. (1995) 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplantation*, **15,** 825–828.

Raiola, A.M., Dominietto, A., Ghiso, A., Di Grazia, C., Lamparelli, T., Gualandi, F., Bregante, S., Van Lint, M.T., Geroldi, S., Luchetti, S., Ballerini, F., Miglino, M., Varaldo, R. & Bacigalupo, A. (2013) Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **19,** 117–122.

Raiola, A.M., Dominietto, A., di Grazia, C., Lamparelli, T., Gualandi, F., Ibatici, A., Bregante, S., Van Lint, M.T., Varaldo, R., Ghiso, A., Gobbi, M., Carella, A.M., Signori, A., Galaverna, F. & Bacigalupo, A. (2014) Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **20,** 1573–1579.

Raj, K., Eikema, D.-J., McLornan, D.P., Olavarria, E., Blok, H.-J., Bregante, S., Ciceri, F., Passweg, J., Ljungman, P., Schaap, N., Carlson, K., Zuckerman, T., de Wreede, L.C., Volin, L., Koc, Y., Diez-Martin, J.L., Brossart, P., Wolf, D., Blaise, D., Bartolomeo, P.D., et al (2018) Family Mismatched Allogeneic Stem Cell Transplantation for Myelofibrosis: Report from the Chronic Malignancies Working Party of European Society for Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*.

Raj, K., Pagliuca, A., Bradstock, K., Noriega, V., Potter, V., Streetly, M., McLornan, D., Kazmi, M., Marsh, J., Kwan, J., Huang, G., Getzendaner, L., Lee, S., Guthrie, K.A., Mufti, G.J. & O'Donnell, P. (2014) Peripheral blood hematopoietic stem cells for transplantation of hematological diseases from related, haploidentical donors after reduced-intensity conditioning. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **20,** 890–895.

Robin, M., Tabrizi, R., Mohty, M., Furst, S., Michallet, M., Bay, J.-O., Cahn, J.-Y., De Coninck, E., Dhedin, N., Bernard, M., Rio, B., Buzyn, A., Huynh, A., Bilger, K., Bordigoni, P., Contentin, N., Porcher, R., Socié, G. & Milpied, N. (2011) Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). *British Journal of Haematology*, **152,** 331–339.

Robin, M., de Wreede, L.C., Wolschke, C., Schetelig, J., Eikema, D.-J., Van Lint, M.T., Knelange, N.S., Beelen, D., Brecht, A., Niederwieser, D., Vitek, A., Bethge, W., Arnold, R., Finke, J., Volin, L., Yakoub-Agha, I., Nagler, A., Poiré, X., Einsele, H., Chevallier, P., et al (2019) Long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis. *Haematologica*.

Rondelli, D., Goldberg, J.D., Isola, L., Price, L.S., Shore, T.B., Boyer, M., Bacigalupo, A., Rambaldi, A., Scarano, M., Klisovic, R.B., Gupta, V., Andreasson, B., Mascarenhas, J., Wetzler, M., Vannucchi, A.M., Prchal, J.T., Najfeld, V., Orazi, A., Weinberg, R.S., Miller, C., et al (2014) MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. *Blood*, **124,** 1183–1191.

Sakellari, I., Mallouri, D., Gavriilaki, E., Batsis, I., Kaliou, M., Constantinou, V., Papalexandri, A., Lalayanni, C., Vadikolia, C., Athanasiadou, A., Yannaki, E., Sotiropoulos, D., Smias, C. & Anagnostopoulos, A. (2017) Survival Advantage and Comparable Toxicity in Reduced-Toxicity Treosulfan-Based versus Reduced-Intensity Busulfan-Based Conditioning Regimen in Myelodysplastic Syndrome and Acute Myeloid Leukemia Patients after Allogeneic Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **23,** 445–451.

Sciumè, M., Mattiello, V., Cattaneo, D., Bucelli, C., Orofino, N., Gandolfi, L., Pettine, L., Lonati, S., Gianelli, U., Pierini, A., Cortelezzi, A. & Iurlo, A. (2017) Early detection of pulmonary hypertension in primary myelofibrosis: The role of echocardiography, cardiopulmonary exercise testing, and biomarkers. *American Journal of Hematology*, **92,** E47–E48.

Shaw, B.E. (2017) Related haploidentical donors are a better choice than matched unrelated donors: Counterpoint. *Blood Advances*, **1,** 401–406.

Shimoni, A., Shem-Tov, N., Volchek, Y., Danylesko, I., Yerushalmi, R. & Nagler, A. (2012) Allo-SCT for AML and MDS with treosulfan compared with BU-based regimens: reduced toxicity vs reduced intensity. *Bone Marrow Transplantation*, **47,** 1274–1282.

Sorror, M.L., Maris, M.B., Storb, R., Baron, F., Sandmaier, B.M., Maloney, D.G. & Storer, B. (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*, **106,** 2912–9.

Tremblay, D., Putra, J., Vogel, A., Winters, A., Hoffman, R., Schiano, T.D., Fiel, M.I. & Mascarenhas, J.O. (2019) The Implications of Liver Biopsy Results in Patients with Myeloproliferative Neoplasms Being Treated with Ruxolitinib. *Case Reports in Hematology*, **2019,** Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6339753/ [Accessed April 19, 2019].

Yerushalmi, R., Shem-Tov, N., Danylesko, I., Avigdor, A., Nagler, A. & Shimoni, A. (2015) Fludarabine and treosulfan compared with other reduced-intensity conditioning regimens for allogeneic stem cell transplantation in patients with lymphoid malignancies. *Bone Marrow Transplantation*, **50,** 1526–1535.

18 LIST OF ADDENDA

18.1 List of Investigators

18.2 Serious Adverse Events report form

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

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par fax au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail.
NB : Ne pas transmettre par fax les documents initialement transmis avec succès par mail pour éviter les doublons

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

1. Identification de la recherche	
Acronyme : **FIBRAPLO**	**Date de notification :** |__|__| |__|__| |2|0|__|__| jj mm aaaa
Code de la Recherche : APHP190648	**Date de prise de connaissance de l'EIG par l'investigateur :** |__|__| |__|__| |2|0|__|__| jj mm aaaa
Risque : D	
Titre complet de la recherche : Allogreffe haplo-identique pour les patients atteints de myélofibrose primitive ou secondaire	

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

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

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 (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*

.....Trecondi© (Treosulfan).....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Fludarabine	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Thiotepa	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Médicament(s) auxiliaire(s) utilisé(s) pour les besoins de la recherche [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 (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Cyclosporine	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Mycophénolate mofetil	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Cyclophosphamide	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

6. Préparation de thérapie cellulaire/tissu/organe administré avant la survenue de l'évènement ***(barrer l'encadré si non applicable)***

Nom du produit expérimental (CSH, CSM, USP, tissu, organe, préciser)	Voie *(1)* *(si applicable)*	Nombre de cellules administrées / Dose *(si applicable)*	Heure de début	En cours *(2)*	Heure de fin
Greffe de CSH		|__|__|__|__|	|__|__| hh |__|__| min	☐	|__|__| hh |__|__| min

7. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

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

⇨ Annexe jointe au présent formulaire : ☐ Oui ☐ Non

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

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

Acronyme : **FIBRAPLO**

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

9. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

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

Organe(s) concerné(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

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

☐ Autre(s) critère(s) médicalement significatif(s), préciser :

.....
.....

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME

☐ arrêt définitif du ME

☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|

☐ ne sais pas

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

○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

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

L'évènement a-t-il conduit à une levée d'insu ?

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

Degré de sévérité *:*

Selon CTCA-AE Toxicity Grading Scale, v5.0:

☐ Grade 1 ☐ Grade 2 ☐ Grade 3

☐ Grade 4 ☐ Grade 5

Selon modified Glucksberg classification for acute GvHD:

☐ Grade 1 ☐ Grade 2 ☐ Grade 3

☐ Grade 4

L'évènement fait-il suite à :

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

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme : **FIBRAPLO**

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

Evolution de l'événement

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

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

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

☐ **Evolution inconnue**

11. Autre(s) étiologie(s) envisagée(s)

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

12. Examen(s) complémentaire(s) réalisé(s)

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

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

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s) expérimental(aux) (ME) / produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**
Lequel : Trecondi© (Treosulfan) ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **au(x) médicament(s) auxiliaire(s) : le(s)quel(s) ?**
Lequel : Cyclosporine ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
Lequel : Mycophénolate mofetil ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
Lequel : Cyclophosphamide ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
La/lequel(le) : Greffe de CSH..... ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
La/lequel(le) : ..... ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

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

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

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

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre ce formulaire au secteur Vigilance par fax au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail.

1. Identification de la recherche

Acronyme : **FIBRAPLO**
Code de la recherche : **APHP 190648**

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 : Allogreffe haplo-identique pour les patients atteints de myélofibrose primitive ou secondaire

2. Identification du centre investigateur

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

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

3. Identification de la personne présentant une grossesse

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

Date de naissance : |__|__| |__|__|__|__|

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

Date de la greffe : |__|__| |__|__| |2|0|__|__| |__|__| |__|__| NA ☐ (si applicable) (jj mm aaaa hh min)

Date des dernières règles : |__|__| |__|__| |2|0|__|__|

Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

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

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

Date de naissance : |__|__| |__|__|__|__|

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

Date de randomisation : |__|__| |__|__| |2|0|__|__|

Expositions au cours de la grossesse :

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

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

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

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

FIBRAPLO

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

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

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

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration[(1)]	Posologie / 24h
Trecondi© (Treosulfan)……	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Fludarabine	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Thiotepa	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

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

6. Médicament(s) auxiliaire(s) utilisé(s) pour les besoins de la recherche et administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

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

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

7. Préparation de thérapie cellulaire/tissu/organe administré avant la survenue de l'évènement ***(barrer l'encadré si non applicable)***

Nom du produit expérimental (CSH, CSM, USP, tissu, organe, préciser)	Voie *(1) (si applicable)*	Nombre de cellules administrées / Dose *(si applicable)*	Heure de début	En cours *(2)*	Heure de fin
Greffe de CSH		|__|__|__|	|__|__| hh |__|__| min	☐	|__|__| hh |__|__| min

8. 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_|__|__|		

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

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

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

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

10. Suivi de la grossesse

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

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

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

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

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

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

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

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

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

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

Sexe : ☐ Masculin ☐ Féminin
Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm
APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

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

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

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

Notificateur	**Investigateur**	Tampon du service :

Nom et fonction : Signature :	Nom : Signature :	

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

Ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI
Par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre ce formulaire de notification d'EIG au secteur Vigilance par fax au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail.
NB : Ne pas transmettre par fax les documents initialement transmis avec succès par mail pour éviter les doublons

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

1. Identification de la recherche

Acronyme : **FIBRAPLO**

Code de la Recherche : APHP190648

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

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__|
jj mm aaa
a

Titre complet de la Recherche :
Allogreffe haplo-identique pour les patients atteints de myélofibrose primitive ou secondaire

Risque : ☐ A ☐ B ☐ C ☒ D

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

2. Identification du centre investigateur

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

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

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

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

Sexe : ☐ M ☐ F

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

Date de naissance :
|__|__| |__|__|__|__|
m m aaaa

Age : |__|__|__|ans

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

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

Date de la greffe : |__|__| |__|__| |2|0|__|__| |__||__| NA ☐
(si applicable) jj mm aaaa hh min

4. Diagnostic du cancer secondaire/de la myélodysplasie

4.1 Diagnostic clinique :

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

Confirmation histologique : ☐ **Non** ☐ **Oui**

Diagnostic final retenu :

Confirmation cytologique : ☐ **Non** ☐ **Oui**	……
4.2 Grade : (précisez l'échelle de classification ex : TNM)	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ……
4.3 Grade histologique	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV
4.4 Si autre classification, précisez :	
4.5 Antécédents médicaux pertinents : ☐ Non ☐ Oui, précisez :	

Acronyme : **FIBRAPLO**

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

5. Précision de l'imputabilité de l'investigateur

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

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s) expérimental(aux) (ME) / produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**

Lequel : Trecondi© (Treosulfan) ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)
Fludarabine ☐Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)
Thiotepa ☐Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

☐ **au(x) médicament(s) auxiliaire(s) : le(s)quel(s) ?**

Lequel : Cyclosporine ☐Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)
Lequel : Mycophénolate mofetil ☐Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)
Lequel : Cyclophosphamide ☐Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable (non exclue)

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

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

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

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

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

☐ Induction |__|__| |__|__| |_2_|_0_|__|__| (j j m m a a a a)	☐ Consolidation |__|__| |__|__| |_2_|_0_|__|__| (j j m m a a a a)
☐ Post greffe : renseignez la partie 6.2	☐ Maintenance |__|__| |__|__| |_2_|_0_|__|__| (j j m m a a a a)
☐ Autre :	☐ Interphase

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

Nom commercial ou Dénomination Commune International	Date de première administration Ou non administré	Date de dernière administration Ou en cours (2)	Voie d'administration(1)	Posologie / 24h	Lien de causalité avec l'EIG *(Relation selon méthode OMS)*

	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

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

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

☐ Non ☐ Oui, précisez ci-dessous :

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

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

Date de sortie d'aplasie : |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a

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

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

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

Acronyme : **FIBRAPLO**

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

7. Statut de la pathologie initiale à la date de survenue du cancer secondaire/de la myélodysplasie

(Joindre si possible les résultats du dernier myélogramme le cas échéant) **:**

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

8. Traitement du cancer secondaire/de la myélodysplasie

8.1 Hospitalisation(s) :

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

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

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

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

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

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

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

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

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

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

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

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

9. Evolution du cancer secondaire/de la myélodysplasie

9.1 Etat actuel (hors décès)

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

9.2 Evolution fatale

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

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

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

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

18.3 Initial Authorization of Treosulfan (December 2018)

https://www.ema.europa.eu/en/documents/product-information/trecondi-epar-product-information_fr.pdf

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/848829/2018 Corr[1]
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[2] (initial authorisation)

Trecondi

treosulfan

On 13 December 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Trecondi, intended for the conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT). Trecondi was designated as an orphan medicinal product on 23 February 2004. The applicant for this medicinal product is medac Gesellschaft fur klinische Spezialpraparate mbH.

Trecondi will be available as a 50 mg/ml powder for solution for infusion. The active substance of Trecondi is treosulfan, a prodrug of an alkylating agent with cytotoxic activity against haematopoietic precursor cells (ATC code: L01AB02).

The benefit with Trecondi is the increase of the rate of event-free survival after 2 years. The most common side effects are infections (bacterial, viral, fungal), stomatitis/mucositis, diarrhoea, nausea, vomiting and abdominal pain.

The full indication is: "Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases."

It is proposed that Trecondi be prescribed by physicians experienced in conditioning treatment followed by alloHSCT.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

[1] The word "injection" has been deleted
[2] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

18.4 SmPC for Fludarabine, Thiotepa, Cyclophosphamide, Mycophenolate mofetil and Cyclosporine

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=69277633&typedoc=R

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=64342415&typedoc=R

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=69116135&typedoc=R

https://ec.europa.eu/health/documents/community-register/2018/20180312140384/anx_140384_fr.pdf

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=62935801&typedoc=R

18.5 ECOG Performance status score (Oken et al, 1982)

indice	description
0	Asymptomatique (activité normale : aucune restriction à poursuivre les activités précédant l'affection).
1	Symptomatique (gêné pour les activités physiques soutenues mais capable de se déplacer seul et d'assurer un travail léger ou sédentaire, par exemple un travail de bureau ou le ménage).
2	Symptomatique, alité moins de 50 % de la journée (capable de se déplacer seul et de s'occuper de soi-même mais incapable de produire un travail léger).
3	Symptomatique, alité plus de 50 % de la journée, sans y être confiné (capable de prendre soin de soi-même de manière limitée, alité ou confiné au fauteuil plus de 50 % de la journée).
4	Confiné au lit (totalement dépendant, incapable de prendre soin de soi-même, confiné au lit ou au fauteuil).
5	Mort.

18.6 Score de comorbidity according to Sorror, 2005(Sorror et al, 2005)

Comorbidity	Definition	Score
Arrhytmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease*, congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Infllammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Pyschiatric discturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Obesity	Patients with a body mass index > 35 kg/m2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rhumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate or severe renal	Serum creatinine > 205 μmol/L, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLco and/or FEV1 66%-80% or dyspnea on slight activity	2
Prior solid tumour	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapsed	3
Severe pulmonary	DLco and/or FEV1 < 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

*One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.

18.7 MF-SAF form: Myelofibrosis Screening Symptom Form according to Mesa(Mesa et al, 2013)

Vous devez répondre à toutes les questions de mémoire sur les **7 derniers jours** (1 semaine) du mieux que vous pouvez. Il n'y a pas de **bonnes ou de mauvaises réponses**.

Nous vous demandons d'évaluer vos symptômes où:

- 0 est l'absence total de symptômes,

-1 à 10, définie l'intensité de vos symptômes sachant que 10 correspond aux symptômes les plus intenses que vous poussiez imaginer. Vous évaluerez le symptôme qui vous a semblé être le pire dans les 7 derniers jours.

Symptômes en rapport avec la myélofibrose	**Echelle d'intensité**
1. Depuis 7 jours, comment évaluez vous vos sueurs nocturnes ?	0 (Absentes) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
2. Depuis 7 jours, comment évaluez vous vos démangeaisons ?	0 (Absentes) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
3. Depuis 7 jours, comment évaluez vous votre inconfort abdominal (ballonnement, douleurs) ?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
4. Depuis 7 jours, comment évaluez vous vos douleurs sous les côtés du côté gauche ?	0 (Absentes) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
5. Depuis 7 jours, comment évaluez vous votre inconfort gastrique après manger (impression de satiété précoce) ?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
6. Depuis 7 jours, comment évaluez vous vos douleurs musculaires ou osseuses diffuses (en dehors de douleurs aux articulations) ?	0 (Absentes) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)
7. Depuis 7 jours, comment évaluez vous les repercussions de votre myélofibrose sur vos activités incluant vos activités professionnelles, sociales et familiales?	0 (Aucune répercussion) 1 2 3 4 5 6 7 8 9 10 (le pire imaginable)

18.8 Acute GVHD classification (Glucksberg adapted by Pzie(Przepiorka et al, 1995)

Stage	Skin	Liver	Gut
0	No rash	Bilirubin < 34 µmol/L	Diarrhea < 500 mg/day
1	Maculo-papular rash < 25% of body surface	Bilirubin 34-50 µm/L	Diarrhea ≤ 1000 ml / j Or nausea vomiting with a positive gut biopsy
2	Maculo-papular rash 25 à 50% of body surface	Bilirubin 51-102 µm/l	Diarrhea > 1000 ml / j
3	Generalized erythroderma	Bilirubin 103-255 µm/l	Diarrhea > 1500 ml / j
4	Generalized erythroderma with bullus and desquamation	Bilirubin > 255 µm/L	Diarrhea ≥ 2000 ml / j

GRADE	SKIN STAGE	GUT STAGE	LIVER STAGE
I	1 à 2	0	0
II	0 à 3	0-1	0-1
III	0 à 3	2-4	0-4
IV	0 à 3*	2-4*	0-4*

*similar to grade III with extreme decrease in clinical performance

18.9 Chronic GVHD classification according to revised Seattle classification (Lee et al, 2003)

Original Seattle Classification	Revised Seattle Classification*
Limited	Clinical limited
One or both of:	1. Oral abnormalities consistent with chronic GVHD, a positive skin or lip biopsy, and no other manifestations of chronic GVHD
Localized skin involvement	2. Mild liver test abnormalities (alkaline phosphatase ≤2 × upper limit of normal, AST or ALT ≤3 × upper limit of normal, and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of chronic GVHD
Hepatic dysfunction due to chronic GVHD	3. Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of BSA, dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of chronic GVHD
	4. Ocular sicca (Schirmer's test ≤5 mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of chronic GVHD
	5. Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of chronic GVHD
Extensive	Clinical extensive
One of:	1. Involvement of 2 or more organs with symptoms or signs of chronic GVHD, with biopsy documentation of chronic GVHD in any organ
Generalized skin involvement	2. Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections not due to other causes, with biopsy documentation of chronic GVHD in any organ
Localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus:	3. Skin involvement more extensive than defined for clinical limited chronic GVHD, confirmed by biopsy
Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or:	4. Scleroderma or morphea
	5. Onycholysis or onychodystrophy thought to represent chronic GVHD, with documentation of chronic GVHD in any organ
Involvement of eye (Schirmer's test with <5 mm wetting), or:	6. Decreased range of motion in wrist or ankle extension due to fasciitis caused by chronic GVHD
	7. Contractures thought to represent chronic GVHD
Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or:	8. Bronchiolitis obliterans not due to other causes
	9. Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 × upper limit of normal, AST or ALT >3 × upper limit of normal, or total bilirubin >1.6, and documentation of chronic GVHD in any organ
Involvement of any other target organ	10. Positive upper or lower GI biopsy
	11. Fasciitis or serositis thought to represent chronic GVHD and not due to other causes

*Provided by Mary E.D. Flowers and Paul J. Martin, Fred Hutchinson Cancer Research Center.
AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; BSA, body surface area.

18.10 Infections considered in the protocol

-pneumonia

-severe sepsis or septicaemia (other than coagulase negative staphylococcus)

-symptomatic bacteriemia

-arthritis / osteomyelitis

-pyelonephritis or prostatis

-profound abscess

-meningitis or encephalitis

-invasive aspergillosis

-candidemia

-CMV disease

-adenoviral disease

-disseminated viral infections (involving at least 2 organs)

-skin or subcutaneous infections

Data concerning benign or asymptomatic infections will not be collected for the protocol:

-superficial fungal infection (skin, mucous)

-upper respiratory tract infection

-sinusitis

-cystitis

-viral infection requiring pre-emptive treatment

-herpes simplex infection

-VZV infections (except severe form leading to pneumonia)

-CMV reactivation

-EBV reactivation

-adenoviral reactivation

18.11 (b) Dose and Volume of treosulfan solution 0.05 g/mL (reconstituted solution in 0.45% NaCl) based on body surface

surface corporelle (m^2)	dose (g)	volume solution reconstituée à 0,05 g/ml (mL)	surface corporelle (m^2)	dose (g)	volume solution reconstituée à 0,05 g/ml (mL)	surface corporelle (m^2)	dose (g)	volume solution reconstituée à 0,05 g/ml (mL)	surface corporelle (m^2)	dose (g)	volume solution reconstituée à 0,05 g/ml (mL)
1,2	12	240	1,65	16,5	330	2,1	21	420	2,55	25,5	510
1,21	12,1	242	1,66	16,6	332	2,11	21,1	422	2,56	25,6	512
1,22	12,2	244	1,67	16,7	334	2,12	21,2	424	2,57	25,7	514
1,23	12,3	246	1,68	16,8	336	2,13	21,3	426	2,58	25,8	516
1,24	12,4	248	1,69	16,9	338	2,14	21,4	428	2,59	25,9	518
1,25	12,5	250	1,7	17	340	2,15	21,5	430	2,6	26	520
1,26	12,6	252	1,71	17,1	342	2,16	21,6	432	2,61	26,1	522
1,27	12,7	254	1,72	17,2	344	2,17	21,7	434	2,62	26,2	524
1,28	12,8	256	1,73	17,3	346	2,18	21,8	436	2,63	26,3	526
1,29	12,9	258	1,74	17,4	348	2,19	21,9	438	2,64	26,4	528
1,3	13	260	1,75	17,5	350	2,2	22	440	2,65	26,5	530
1,31	13,1	262	1,76	17,6	352	2,21	22,1	442	2,66	26,6	532
1,32	13,2	264	1,77	17,7	354	2,22	22,2	444	2,67	26,7	534
1,33	13,3	266	1,78	17,8	356	2,23	22,3	446	2,68	26,8	536
1,34	13,4	268	1,79	17,9	358	2,24	22,4	448	2,69	26,9	538
1,35	13,5	270	1,8	18	360	2,25	22,5	450	2,7	27	540
1,36	13,6	272	1,81	18,1	362	2,26	22,6	452	2,71	27,1	542
1,37	13,7	274	1,82	18,2	364	2,27	22,7	454	2,72	27,2	544
1,38	13,8	276	1,83	18,3	366	2,28	22,8	456	2,73	27,3	546
1,39	13,9	278	1,84	18,4	368	2,29	22,9	458	2,74	27,4	548
1,4	14	280	1,85	18,5	370	2,3	23	460	2,75	27,5	550
1,41	14,1	282	1,86	18,6	372	2,31	23,1	462	2,76	27,6	552
1,42	14,2	284	1,87	18,7	374	2,32	23,2	464	2,77	27,7	554
1,43	14,3	286	1,88	18,8	376	2,33	23,3	466	2,78	27,8	556
1,44	14,4	288	1,89	18,9	378	2,34	23,4	468	2,79	27,9	558
1,45	14,5	290	1,9	19	380	2,35	23,5	470	2,8	28	560
1,46	14,6	292	1,91	19,1	382	2,36	23,6	472	2,81	28,1	562
1,47	14,7	294	1,92	19,2	384	2,37	23,7	474	2,82	28,2	564
1,48	14,8	296	1,93	19,3	386	2,38	23,8	476	2,83	28,3	566
1,49	14,9	298	1,94	19,4	388	2,39	23,9	478	2,84	28,4	568
1,5	15	300	1,95	19,5	390	2,4	24	480	2,85	28,5	570
1,51	15,1	302	1,96	19,6	392	2,41	24,1	482	2,86	28,6	572
1,52	15,2	304	1,97	19,7	394	2,42	24,2	484	2,87	28,7	574
1,53	15,3	306	1,98	19,8	396	2,43	24,3	486	2,88	28,8	576
1,54	15,4	308	1,99	19,9	398	2,44	24,4	488	2,89	28,9	578
1,55	15,5	310	2	20	400	2,45	24,5	490	2,9	29	580
1,56	15,6	312	2,01	20,1	402	2,46	24,6	492	2,91	29,1	582
1,57	15,7	314	2,02	20,2	404	2,47	24,7	494	2,92	29,2	584
1,58	15,8	316	2,03	20,3	406	2,48	24,8	496	2,93	29,3	586
1,59	15,9	318	2,04	20,4	408	2,49	24,9	498	2,94	29,4	588
1,6	16	320	2,05	20,5	410	2,5	25	500	2,95	29,5	590
1,61	16,1	322	2,06	20,6	412	2,51	25,1	502	2,96	29,6	592
1,62	16,2	324	2,07	20,7	414	2,52	25,2	504	2,97	29,7	594
1,63	16,3	326	2,08	20,8	416	2,53	25,3	506	2,98	29,8	596
1,64	16,4	328	2,09	20,9	418	2,54	25,4	508	2,99	29,9	598
									3	30	600