JAK ALLO STUDY

JAK2 inhibitors RUXOLITINIB in patients with high or intermediate risk primary or secondary myelofibrosis eligible for allogeneic stem cell transplantation: a prospective multicentric phase II study

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I. Synopsis

A. French version

Titre court	**JAK – ALLO**
Titre descriptive	**Inhibiteurs de JAK2 RUXOLITINIB avant allogreffe de cellules souches hématopoïétiques pour les patients atteints de myélofibrose primitive ou secondaire : étude prospective multicentrique de phase II**
Numérod'étude	
Promoteur	**GOELAMS**
Groupescollaborateurs	**FIM** **SFGM-TC**
Phase	**II**
Population	Patients atteints de myélofibrose et potentiels candidats à l'allogreffe
Rationnel	Jusqu'à maintenant, l'allogreffe de CSH est le seul traitement curateur pour les patients atteints de myélofibrose(Ballen*, et al*, Guardiola*, et al* 1999, Kroger*, et al* 2007). L'allogreffe permet de guérir 30 à 70% des patients selon le stade de la maladie, l'âge du patient, les comorbidités du patient, l'état général du patient et le type d'allogreffe. La prise de greffe, qui est de 70 à 95% dans cette maladie, est largement influencée par la taille de la rate pré-greffe. L'étude Française de la SFGM-TC a montré que la taille pré-greffe de la rate influence la survie postgreffe(Robin*, et al*), une étude italienne corrobore ces résultats (Bacigalupo*, et al*). En vue d'améliorer la prise de greffe et les résultats de l'allogreffe, en France, 40% des patients avec splénomégalie volumineuse sont splénectomisés en pré-greffe. Malheureusement, la splénectomie s'accompagne de morbidité et mortalité non négligeable (Mesa*, et al* 2006). Les inhibiteurs de JAK2 et notamment le ruxolitinib a montré que la majorité des patients atteints de myélofibrose améliorait leur état général et diminuait de plus de 50% leur splénomégalie (Verstovsek*, et al*). Ces effets très positifs seraient très profitables pour les candidats à la greffe car permettraient aux patients d'être allogreffés avec un meilleur état général, dont on sait que c'est un facteur important pour la réussite de la greffe, et avec une rate moins volumineuse, évitant ainsi la splénectomie pré-greffe. De plus, les inhibiteurs de JAK2 semblent agir au niveau de certaines cytokines, ce qui

	pourrait atténuer « l'orage cytokinique » décrit en postallogreffe et à l'origine de toxicité aiguë et de réaction immunologique aiguë. En conséquence, les patients traités par inhibiteurs de JAK2 en prégreffe devraient avoir une mortalité diminuée par rapport aux patients non traités. L'étude que nous proposons consiste à tester la tolérance et l'efficacité des inhibiteurs de JAK2 avant l'allogreffe de CSH pour tous les patients potentiellement candidats à l'allogreffe.
Comparaison des patients en fonction de la disponibilité d'un donneur	Dès que les patients ont une indication d'allogreffe du fait de l'évolution de leur maladie et une fois qu'une contre indication à l'allogreffe a bien été éliminée, les patients peuvent être inclus dans l'étude avant même de savoir s'il existe des donneurs HLA compatibles dans la famille ou sur fichier. Le traitement est débuté dès l'inclusion du patient et les recherches de donneur sont faites simultanément. De ce fait, certains patients auront un donneur et pourront bénéficier d'une allogreffe alors que d'autres patients ne seront jamais greffés, faute de donneur. On estime qu'environ 70% des patients auront des donneurs, parmi ces patients, une majorité (> 80%) bénéficiera effectivement de l'allogreffe alors que certains pourront acquérir une contre indication à la greffe ou malheureusement décéder pendant le délai nécessaire à la recherche de donneur et au traitement par RUXOLITINIB.
Nombre de sites	20 à 30 centres Français, Belges et Suisses participeront à l'étude
Nombre de patients attendus	Les inclusions seront terminées lorsque 53 patients seront transplantés. Le nombre total d'inclusion est estimé à 80 patients.
Objectif principal	L'objectif principal qui ne concerne que les 53 patients recevant effectivement une allogreffe est d'observer une survie sans rechute à 12 mois de l'allogreffe supérieure à 50%.
Objectifs secondaires	1. Patients allogreffés seulement • Calcul du taux de patients avec donneur bénéficiant d'une allogreffe • Calcul du taux de splénectomie prégreffe • Calcul du score de comorbidité prégreffe défini par Sorror et al avant traitement par le RUXOLITINIB et avant allogreffe • Etude de la reconstitution hématologique postgreffe : délai de prise pour les neutrophiles, indépendance transfusionnelle pour les hématies et les plaquettes • Etude de l'incidence de GVHD aiguë grade II-IV • Etude de l'incidence de GVHD chronique

	• Etude de la survie globale, la survie sans maladie et la mortalité non liée à la rechute à 18 mois de la greffe Evolution qualitative et quantitative des allèles mutés JAK2 à l'inclusion, 3, 7, 16 mois post inclusion (centralisation à l'hôpital Saint-Louis)
Objectifs secondaires	2. Patients avec ou sans donneur • Evolution du score de comorbidité à l'inclusion et à 3 mois de traitement • Acquisition d'uneindépendancetransfusionnelle • Evolution de l'état général (ECOG) • Evolution des signes généraux liés à la myélofibrose (questionnaire MF SAF) • Comparaison du taux de réponse hématologique avec ou sans donneur • Evolution de la taille de la rate • Comparaison de la qualité de vie des patients avec et sans donneur (questionnaire EORTC) • Comparaison de la survie globale des patients avec et sans donneur • Etude des incidences d'infectionsévère • Etude biologique des sécrétions cytokiniques à l'inclusion, 3 et 7 mois après l'inclusion 3. Statut MPL à l'inclusion
Modalités de prescription de l'inhibiteur de JAK2	Les patients recevront le RUXOLITINIB dès l'inclusion dans l'étude, à raison de 15 mg (3 comprimés de 5 mg) deux fois par jour per os. Un ajustement est prévu en cas de cytopénie ou de réponse insuffisante. Sauf intolérance, les patients recevront au minimum 4 mois de traitement par le RUXOLITINIB. Le RUXOLITINIB sera diminué progressivement puis arrêté la veille du conditionnement de l'allogreffe. 4. En cas de progression ou non efficacité pour les patients non allogreffés, le RUXOLITINIB sera également arrêté.

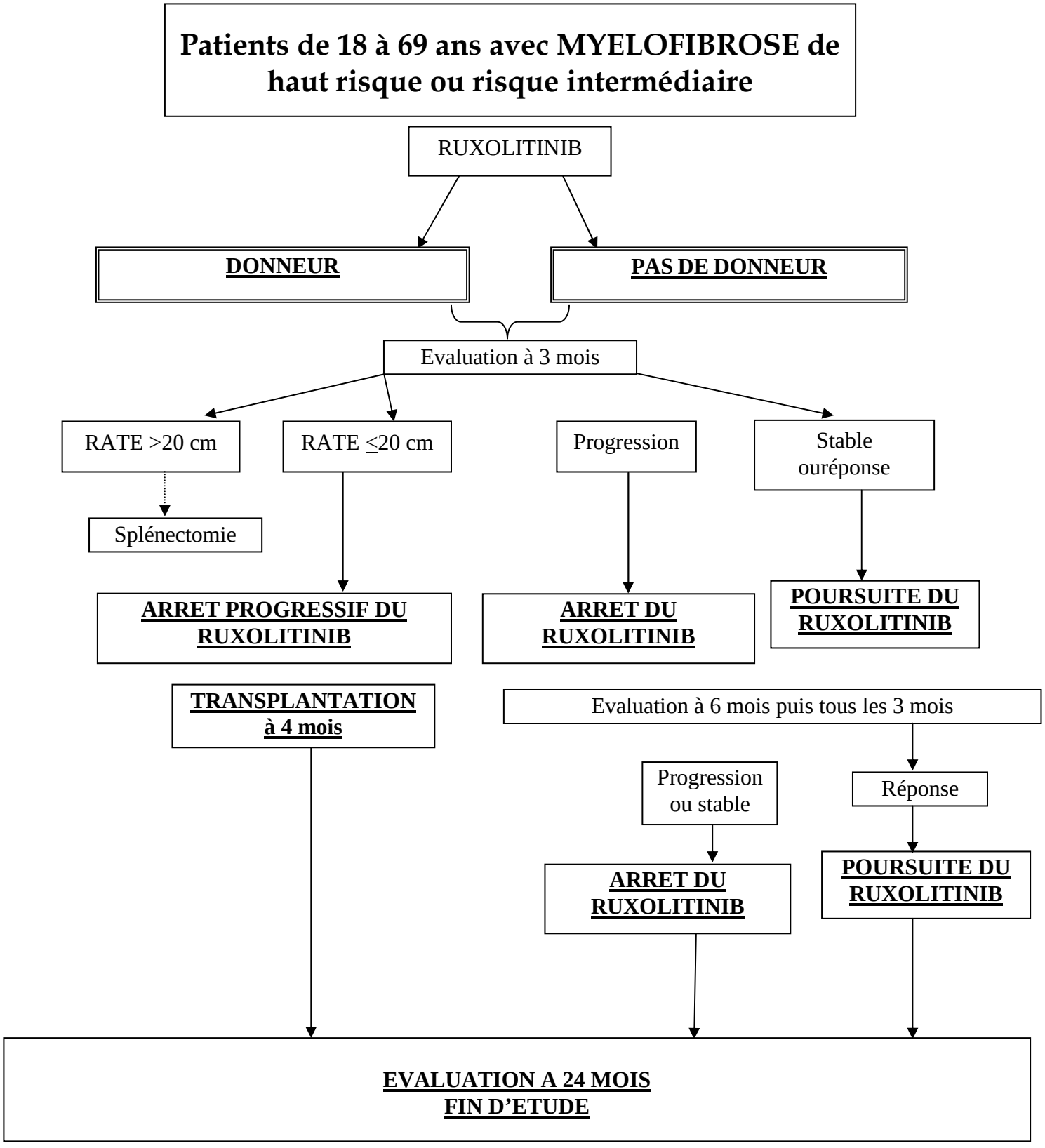
Stratégie de choix du donneur	A l'inclusion, un typage HLA est effectué en vue de rechercher un donneur. La fratrie sera testée en priorité et le cas échéant, une inscription sur fichier international sera faite. Les donneurs HLA identiques de la fratrie et les donneurs non apparentés ayant en haute résolution 10 identités HLA sur 10 avec le receveur (HLA –A, -B, -C, -DRB1, -DQB1) pourront être choisis. A défaut, un donneur ayant 9 identités HLA sur 10 (en haute resolution) pourra également être choisi. Les sangs placentaires ne font pas partie des sources de cellules souches hématopoïétiques acceptées dans ce protocole.
Modalités d'allogreffe	L'allogreffe sera réalisée après un conditionnement « intermédiaire » de type alkylant et fludarabine dans les 4 à 6 mois qui suivent l'inclusion : FLUDARABINE 90mg/m2 dose totale en 3 jours et MELPHALAN 140 mg/m2 dose totale sur un jour. Du sérum anti-lymphocytaire sera ajouté si le donneur a une incompatibilité HLA (9/10^{e}) La source de cellules sera préférentiellement des cellules souches périphériques mais la moelle osseuse est autorisée. La prophylaxie de la GVHD sera assurée par l'association de ciclosporine et mycophenolatemofetil. Les prophylaxies anti-infectieuses seront standard et pourront variées légèrement d'un centre à l'autre, elle devra comprendre une prophylaxie contre l'Herpes simplex, la toxoplasmose et la pneumocystose.
Durée de participation des patients	Après inclusion, les patients seront suivis pendant 24 mois, incluant une période de suivi postgreffe d'environ 16 à 20 mois selon les patients (selon la date de greffe théoriquement prévue à 4 mois).
Durée de l'étude	La durée d'inclusion est estimée à 24 mois. La durée de suivi des patients est de 24 mois. La durée totale prévisible de l'étude est de 48 mois.

Critères d'inclusion	**1. Liés au patient** • Age compris entre 18 et 69 ans • Absence de comorbidités contre indiquant habituellement la greffe : o Insuffisance respiratoire sévère définie par une dyspnée de stade > II o Insuffisance cardiaque sévère définie par une FEVG < ou = à 30% o Insuffisance rénale sévère définie par une clairance de la créatinine < 30 ml/min ou une dialyse o Démence ou conditions intellectuelles ne permettant pas de donner son accord pour un protocole de recherche clinique o Altération majeure de l'état général définie par un ECOG > 2 o Atteinte hépatique sévère définie par le diagnostic d'une cirrhose, une bilirubine > 2 x la norme haute, ou des AST/ALT > 5 x la norme haute **2. lié à la maladie** • Myélofibrose primaire ou secondaire diagnostiquée selon les définitions OMS habituelles (Tefferi, *et al* 2007) • Splénomégalie palpable ou taille du plus grand diamètre > 15cm en imagerie (échographie/IRM/TDM) • Maladie à risque intermédiaire ou élevé défini selon les critères publiés et résumés ci-dessous : <u>Au moins un critère parmi les suivants</u> : -Hémoglobine < 100 gr/L (en dehors de toxicité médicamenteuse) -Leucocytes < 4 G/L (en dehors de toxicité médicamenteuse) ou > 25 G/L -Anomalie cytogénétique de mauvais pronostic : caryotype complexe, anomalie des chromosomes 5, 7 ou 17 <u>Les 2 critères suivants ensembles</u> : -Symptômes généraux (perte de poids > 10% en moins de 6 mois, sueurs nocturnes, fièvre spécifique > 37.5) -Blastose sanguine > 1% constatée au moins à 2 reprises à 1 semaine d'intervalle

Critèresd'exclusion	• Myélofibrose transformée en leucémie aiguë avec 20% de blastes ou plus dans le sang ou dans la moelle osseuse • Traitement préalable par inhibiteurs de JAK2 • Thrombopénie< 50 G/L • Comorbiditéscontreindiquant la greffe • Score de comorbidité selon Sorror> 3 • Femme enceinte ou allaitant
Calcul statistique de l'effectif	Il est raisonnable de considérer que les taux de survie sans maladie habituels à 12 mois d'une allogreffe de CSH chez ces patients est de 50% sans inhibiteur de JAK2, puisque c'est la survie de la cohorte française et d'autres cohortes. Si l'hypothèse est que la probabilité de survie sans maladie passe de 50% à 70% grâce à l'inhibiteur utilisé en prégreffe avec une erreur alpha unilatérale de type I de 5% et une puissance de 90% selon la formule de A'Hern'sformul, 53 patients allogreffés seront nécessaires pour démontrer cet hypothèse. L'analyse sera basée sur un test binomial comparant la survie sans maladie à 12 mois de 50%. La probabilité d'identifier un donneur pour les patients français est d'environ 70%. Le nombre de patients à inclure permettant d'atteindre le nombre de 53 patients est d'environ 80. Un des objectifs secondaires étant de comparer la survie et la réponse hématologique des patients avec ou sans donneur, l'hypothèse selon laquelle une rémission hématologique complète de 50% pour les patients allogreffés contre 10% des patients non allogreffés pourra être également testée avec une puissance de 80%.
Règlesd'arrêt du protocole	Une mortalité à 60 jours de l'allogreffe excessive atteignant 15% est jugée inacceptable dans le protocole et se soldera pas un arrêt définitif des inclusions**.**

Méthodestatistique	L'analyse principale reposera sur une comparaison du taux de survie sans maladie à 12 mois à 50% par un test binomial. Des courbes de survie globale et de survie sans maladie ainsi que les incidences cumulées d'infection, d'indépendance transfusionnelle, de réaction de greffon contre l'hôte et de mortalité non liée à la rechute seront estimées, et comparées entre les groupes de patients avec et sans donneur. Pour les patients greffés, des facteurs associés à la survie sans maladie seront recherchés à l'aide de modèles à risque proportionnel de Cox.
Evènementsindésirables	Les évènements indésirables graves seront reportés sur les formulaires SAE et les SUSAR seront déclarés dans Eudravigilance, aux comités d'éthique et autorités compétentes concernés.
Comité indépendant de surveillance	Un comité indépendant de surveillance se réunira régulièrement et pourra décider de stopper le traitement en fonction des effets indésirables constatés.

Schéma de l'étude JAK ALLO



English synopsis

Short title	**JAK – ALLO**
Descriptive title	**JAK2 inhibitor RUXOLITINIB before allogeneic hematopoietic stem cell transplantation (HSCT) in patients with primary or secondary myelofibrosis : a prospective phase II**
Study number	
Sponsor	**GOELAMS**
Collaborative groups	**FIM** **SFGM-TC**
Phase	**II**
Population	Patients with myelofibrosis and potentially candidates for allogeneic transplantation
Rational	Until now, HSCT remains the only curative treatment in patients with myelofibrosis (Ballen*, et al*, Guardiola*, et al* 1999, Kroger*, et al* 2007). HSCT is able to cure 30 to 70% of patients according to disease stage, age of patient, comorbidities, performance status and type of transplantation. Engraftment, which is 70 to 95% in this disease is influenced by pregraft spleen size. The French study showed that pregraft spleen size has also an impact on survival (Robin*, et al*), an Italian study showed similar results (Bacigalupo*, et al*). In order to improve engraftment and general outcome after HSCT, in France, 40% of patients with myelofibrosis are splenectomized before transplantation. Unfortunately, splenectomy significantly induces morbidity and mortality (Mesa*, et al* 2006). JAK2 inhibitors, particularly the ruxolitinib showed that the majority of patients with myelofibrosis improve their performance status and have a reduction of spleen size > 50% (Verstovsek*, et al*). These very favourable effects can be very positive for patients who are candidates for HSCT allowing a better performance status at time of HSCT which can impact postHSCT outcome. Furthermore, a smaller spleen can avoid the pre-transplant splenectomy and its risk. JAK2 inhibitors can also decrease some inflammatory cytokine levels, reducing the "cytokinic storm" described early after HSCT and appearing connected to acute toxicity and graft-versus-host disease (GVHD). Consequently, patients treated with JAK2 inhibitors before transplantation should have a decreased mortality in comparison to patients not treated. We propose a study testing the tolerance and efficacy of RUXOLITINIB in patients with myelofibrosis who are potential candidates for transplantation.

Comparison of patients according to donor availability	As soon as the patient has an indication for HSCT because of disease progression and if there is no contraindication for HSCT, he can be included before knowing the availability of an HLA compatible sibling or unrelated donor. RUXOLITINIB is started after inclusion and the research of the HLA compatible donors are begun concomitantly. Some patients will have a donor and will be transplanted and other patients will not have a donor and will not be transplanted. We estimated that 70% of patients will have a donor and a majority (> 80%) of them will benefit from a transplantation whereas some of them will acquire a contraindication to transplantation or die during donor research or RUXOLITINIB treatment.
Number of sites	20 to 30 centres including French, Belgian or Swiss centres
Number of patients	Inclusions will be stopped once 53 patients are being transplanted The total estimated number of patients is 80.
Primary objective	The primary objective concerns the 53 patients who receive an HSCT. The primary objective is to observe a DFS 12 months after HSCT more than 50%.
Secondary objectives	**Patients who receive a transplantation only:** • Rate of pre-graft splenectomy • Co-morbidity score defined by Sorror et al before RUXOLITINIB and after 4-month treatment just before transplantation • Post-graft haematological recovery: time to neutrophil engraftment, platelet and red blood cells transfusion independency • Acute GVHD grade II-IV incidence • Chronic GVHD incidence • Overall survival, disease-free survival, non-relapse mortality • JAK2V617E allele burden and status at registration, 3, 7, 16 months after inclusion (centralization) **Patients with and without donor:** • Rate of patients with donor who benefit from a transplantation • Comorbidity score at registration and after 3 months • Platelet and red blood cells transfusion independency • Performance status evolution (ECOG) • General symptoms related to myelofibrosis (questionnaire MF SAF)

Secondary objectives (next)	• Comparison of haematological response in patients with or without donor • Spleen size evolution • Comparison of quality of life in patients with and without (questionnaire EORTC) • Comparison of overall survival in patients with and without donor • Incidence of severe infections • Cytokine measure at registration, 3, and 7 months after inclusion (centralization) • MPL JAK status (at registration, centralization)
Prescription of RUXOLITINIB	Patients will receive RUXOLITINIB at time of registration, at the dosage of 15 mg BID per os. Except for stopping of treatment due to intolerance, patients will receive RUXOLITINIB for at least 4 months. Dose adjustment is planned according to tolerance and efficacy. RUXOLITINIB will be stopped one day before conditioning regimen or until progression or non-efficacy for non-transplanted patients
Strategy to choose a donor	At registration, HLA typing will be performed in order to search for a donor. The sibling will be priority tested and if needed a search on international files will be done. HLA identical sibling or matched unrelated donor (10/10 or 9/10 in high resolution HLA) can be chosen. Cord blood source is not accepted in this protocol.
Allograft modalities	HSCT will be performed after a moderately reduced conditioning regimen consisting of “alkylant” and “fludarabine” 4 to 6 months after registration: FLUDARABINE 90mg/m2 total dose and MELPHALAN 140 mg/m2 total dose. Anti-thymoglobulin will be added if the donor shows one HLA mismatch with the recipient. Source of stem cells will be preferentially peripheral stem cells but bone marrow is authorized as stem cell source. Cyclosporine and mycophenolate mofetil wil be used for GVHD prophylaxis.Prophylaxis against infections can vary between centres but should include a prophylaxis against Herpes Simplex, Toxoplasmosis and Pneumocystis.

Patients follow-up duration	After inclusion, patients will receive follow-up for **24 months**, including a postgraft transplant from 16 to 20 months depending from the date of transplantation (from registration).
Study duration	Inclusion phase is estimated for 24 months. Patients follow-up duration is 24 months. The expected total study duration is 48 months.
Inclusion criteria	**1. Related to patients** • Age between 18 and 69 years • No comorbidity contraindicating the transplantation : o Severe respiratory failure defined as dyspnea grade III or more o Severe cardiac failure defined as EF < or = 30% o Severe renal failure defined as creatinine clearance < 30 ml/min or dialysis o Dementia or non-ability to give informed consent for the protocol o Major alteration of performance status defined as ECOG > 2 o Severe liver disease defined as a cirrhosis or bilirubin > 2 x ULN, or AST/ALT > 5 x ULN **2. Related to the disease** • Primary or secondary myelofibrosis diagnosed according to WHO definition (Tefferi, *et al* 2007) • Palpable splenomegaly or splenomegaly measured by any imagery (maximum size> 15 cm by ultrasound scan, Magnetic Resonance Imaging or computer tomography) • Disease if intermediate or high risk according to published criteria and summarized as follows: <u>At least one criterion among</u> the following: -Haemoglobin < 100 gr/L (unrelated to medication toxicity) -Leucocytes < 4 G/L (unrelated to medication toxicity) or > 25 G/L -Poor prognosis cytogenetics : complex karyotype, abnormalities of chromosomes 5, 7 or 17 <u>Combination of both criteria</u> : -General symptoms (weight lost > 10% in less than 6 months, night swears, specific fever > 37.5°C) -Peripheral blastosis > 1% observed at least twice

Exclusion criterias	• Myelofibrosis transformed into acute leukaemia with 20% blasts of more in blood or bone marrow • Previous treatment with JAK2 inhibitor • Thrombopenia < 50 G/L • Comorbidities contraindicating the transplantation • Comorbidity score Sorror > 3 • Pregnant or lactating women
Number of patients for statistical calculation	The primary objective is to demonstrate that DFS 12 months after HSCT is higher than 50% in patients who received a treatment with RUXOLITINIB before HSCT. The trial would be designed to test the hypothesis P $\leq$ 50% versus P$\geq$70% with one sided type I error rate 5% and power 90% with A'Hern's formula, **53 patients should be transplanted**. The analysis will be based on a binomial test comparing the observed 12 months DFS to 50%. **Enrolment will be stopped as soon as 53 patients have received a HSCT**. The probability of finding a donor in French patients is about 70% (HLA matched sibling or unrelated donor with 9 or 10 HLA identities). That means that 80 patients should be included in the study. To respond to one of the secondary objectives of the study, namely, the complete haematological remission, our hypothesis is that 50% of patients with donor compared to 10% in patients without a donor will obtain a complete remission. If the study included 53 patients with donor and 23 patients without donor, the number of patients is sufficient to respond to this objective with power of 80%. The statistical analysis will be done in intent to transplant considering patients with or without donor.
Termination criteria	The maximum acceptable rate of toxic death during the **first 60 days postHSCT will be fixed at 15%**, and the type I error α at 5%.
Statistical analysis	The main analysis will rely on a binomial test comparing the observed 12 months DFS to 50%. Overall survival and disease-free survival curves, as well as cumulative incidence of infection, transfusion independency, graft versus host disease and non-relapse mortality will be estimated, and compared between patients with and without donor. For transplanted patients, factors associated with DFS will be analysed using Cox proportional hazards models.

Adverse events	Serious adverse events will be reported on the SAE form and SUSAR will be declared to Eudravigilance, concerned Ethic committees and concerned Competent Authorities
Data Safety monitoring board	An independent committee will regularly review the trial and can decide to stop the treatment according to toxic events.

Table of content

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ANC	Absolute Neutrophyl Count
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
AUC	Area Under Curve
b.i.d.	*bis in diem*/twice a day
BUN	Blood Urea Nitrogen
CDP	Clinical Development Plan
CTH	Clinical Trial Head
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
CBC	Complete Blood Count
CML	Chronic Myelogenous Leukemia
CRF	Case Report/Record Form;.
Ecrf	Electronic Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CYP	Cytochrome
DDS	Dose-Determining Set
DFS	Disease-free survival
DLT	Dose Limiting Toxicity
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EF	Cardiac Ejection Fraction
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
EPO	Erythropoietin
ET	Essential Thrombocythemia
EWOC	Escalation With Overdose Control
FDP	Fibrinogen Degradation Products
FPFV	First Patient First Visit
GCSF	Granulocyte Colony Stimulating Factor
GGT	Gamma Glutamyl Transpeptidase
GI	Gastrointestinal
GVHD	Graft-versus Host disease

hCG	human Chorionic Gonadotropin
HB	Haemoglobin
HLA	Human Leucocyte Antigen
HSCT	Allogeneic Haematologic Stem Cell Transplantation
IB	Investigator Brochure
ICF	Informed Consent Form
i.v.	Intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IN	Investigator Notification
INR	International Normalized ratio
IPSS	International Prognosis System Score
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IWG	International Working Group,
JAK1	Janus kinase 1
JAK2	Janus kinase 2
LPLV	Last Patient Last Visit
LDH	Lactate deshydrogenase
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation.
MDRD-eGFR	Modification of Diet in Renal Disease estimated Glomerular Filtration Rate
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MPN	Myeloproliferative Neoplasm
MTD	Maximum Tolerated Dose
MSSD	Maximum Safe Starting Dose
NRM	Non-relapse Mortality
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
NONMEM	Non-linear Mixed Effects Modeling
o.d.	*omnia die*/once a day
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PB	Peripheral Blood Stem Cells
PD	Pharmacodynamic
PET-MF	Post Essential Thrombocythemia Myelofibrosis
PFT	Pulmonary Function Test
PHI	Protected Health Information
PK	Pharmacokinetic

PLT	Platelet
PMF	Primary Myelofibrosis
p.o.	*per os*/by mouth/orally
PPV-MF	Post Polycythemia Vera Myelofibrosis
PRBC	Packed Red Blood Cells
PTT	Partial Thromboplastin time
PV	Polycythemia Vera
q.AM	Every morning
q.PM	Every afternoon
QD	Quaque die: once a day
QOL	Quality of Life
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RBC	Red Blood Cells
REB	Research Ethics Board
RIC	Reduced intensity conditioning regimen
SAE	Serious Adverse Event
SAF	Symptom Assessment Form
SFGM-TC	Société Française de Greffe de Moelle et de Thérapie Cellulaire
SOP	Standard Operating Procedure
SSF	Screening Symptom Form
STAT3	Signal transducer and activator of transcription 3
SUSARs	Suspected Unexpected Serious Adverse Reactions
TPO	Thrombopoetin
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

II. Background

A. Diagnosis and prognosis of myelofibrosis

The four classic myeloproliferative neoplasms include chronic myelogenous leukemia (CML), polycythemia Vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Myelofibrosis (MF) can present as a de novo primary disorder (PMF) or evolve secondarily from previous PV or ET (post-PV-MF or post ET-MF). Regardless of whether MF is a primary or secondary disorder, it is characterized by a clonal stem cell proliferation associated with production of elevated serum levels of multiple inflammatory and proangiogenic cytokines, a characteristic bone marrow stromal pattern that includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Clinically, MF is characterized by progressive anemia, leucopoenia or hyperleucocytosis, thrombocytopenia or thrombocythemia and multi-organ extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience severe constitutional symptoms, sequelae of massive splenomegaly (pain, limitations of movement, early satiety and shortness of breath, hepatic obstruction, and spleen infarction), a hypermetabolic state with cachexia, progressive hematopoietic failure, progression to leukemia, and premature death. An expert panel revised recently the 2001 definition of World Health Organization (WHO). The new definition for PMF is given in **Annexe 1** (Tefferi*, et al* 2007).

The median age at diagnosis is approximately 60 to 65 years. The incidence of MF has been estimated at 1.5 cases per 100,000 people. Survival in MF varies with the presence or absence of specific risk factors. Several prognosis scores have been developed. In the 90's, 2 scores have been developed and have been currently used in these patients until a recent update: the Lille score by Dupriez et col (Dupriez*, et al* 1996) and the Cervantes score (Cervantes*, et al* 1998). Both scores can categorize patients with myelofibrosis into low, intermediate and high risk according to blood count for the Lille score and blood count plus general symptoms for the Cervantes score. The International Working group (IWG) for Myelofibrosis Research and Treatment (MRT) has recently published a new score accepted by scientific community as a new International Prognostic System Score (IPSS) in myelofibrosis (Cervantes*, et al* 2009).

Age of greater than 65 years, presence of constitutional symptoms (weight loss > 10% of the baseline value in the year preceding MF diagnosis, unexplained fever, or excessive night sweats persisting for more than 1 month), anemia (hemoglobin (hg) less than 100 g/L), leukocytosis (white blood cell count (WBC) greater than 25 G/L), and a circulating blast percentage of 1% or higher as individually predictive of outcome. They demonstrated that patients could be distinctly grouped into four categories without overlapping median survival curves based upon their number of risk factors (**Table 1**).

Table 1 - Median survival of MF patients according to risk category with factors at time of diagnosis.

No of risk factors	Risk category	Median survival (months)
0	Low	135
1	Intermediate-1	95
2	Intermediate-2	48
3 or more	High	27

Dynamic scores have been also developed in order to test the possible applications of the score during the disease evolution. The IWG-MRT has published a dynamic score including the parameters of the original score which remains prognostic. Furthermore a dynamic score adjusted for age has also been added. This score is particularly adapted in patients who are candidate for transplantation. Calculation of this score is not similar to the static score: WBC > 25 G/L counting one point whereas constitutional symptoms, peripheral blasts > 1% and hemoglobin level < 100 gr/L counting 2 points declining low risk (no risk factor), intermediate 1 risk (1 or 2 points), intermediate 2 risk (3 or 4 points) and high risk (> 4 points). **Table 2** shows survival according to the score (Passamonti*, et al* 2010).

Table 2 –
Median survival of MF patients according to the dynamic IPSS adjusted for age.

No of risk factors	Risk category	Median survival (years)
0	Low	Not reached
1-2	Intermediate-1	9.8
3-4	Intermediate-2	4.8
5 or more	High	2.3

Morel et al have also reported the predictive value of several time dependant variables (Morel, *et al*). They confirmed that hemoglobin and WBC remain predictive for death as considered as time-dependant variables but also PLT count (< 150 G/L) as well as IWG-MRT high or intermediate scores.

Cytogenetic has been also reported as prognostic in patients with myelofibrosis and is abnormal in 40% of MF patients. Some chromosomal aberrations are now considered pejorative for outcome. Very poor outcome (median survival < 6 months) is observed in patients with 17 aberrations and poor outcome is reported in patients with sole + 18, complex karyotype (> 2 abnormalities) or chromosome 5 and/or 7 abnormalities (median survival ranging from 15 to 34 months depending from abnormalities and publications). Among patients with complex karyotype, monosomal karyotype defined as 2 or more autosomal monosomies or a single autosomal monosomy associated with at least 1 structural abnormality, conferred a particularly poor prognosis (median survival at 6 months) (Vaidya, *et al*). More favorable outcomes are seen in patients with normal cytogenetic or other abnormalities (Hussein, *et al*, Tam, *et al* 2009a, Vaidya, *et al*).

B. Inhibition of Janus Kinases (JAK) in Myelofibrosis

A considerable number of cytokine and growth factor receptors utilize non-receptor tyrosine kinases, the Janus kinases (JAK), to transmit extracellular ligand binding into an intracellular response. For example, erythropoietin, thrombopoietin and granulocyte monocyte colony stimulating factor are all known to signal through receptors that utilize *JAK2*. JAK activates a number of downstream pathways implicated in proliferation and survival, including the STATs (signal transducers and activators of transcription), a family of important latent transcription factors.

Myelofibrosis is a clonal stem cell disease characterized by molecular (*JAK2*V617F, *MPL*W515L/K) and cytogenetic markers (Boyd*, et al*, Pardanani*, et al* 2006) (Baxter*, et al* 2005, Jones*, et al* 2005, Levine*, et al* 2005). The *JAK2*V617F mutation has been identified in over 95% of patients with PV and approximately 50% of patients with ET and PMF. Furthermore, in a preclinical setting, animal studies have demonstrated that this mutation can lead to a MF-like syndrome. The *JAK2*V617F mutation alters the *JAK2* tyrosine kinase making it constitutively active. As a result, polycythemia, thrombocythemia and leukocytosis can develop independently from growth factor regulation. Even in patients lacking a confirmed *JAK2* mutation, the detection of STAT activation suggests deregulated *JAK* activity. In fact, regardless of the mutational status of *JAK2*, the malignant cells appear to retain their responsiveness to *JAK* activating cytokines and/or growth factors; and therefore, may benefit from *JAK* inhibition.

C. Non targeted medical treatment

Drug therapies used to treat MF, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and erythropoiesis stimulating agents or growth factors, have not been shown to improve survival. Some can increase the risk of leukemic transformation, and/or are poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. Splenectomy, performed in approximately 10% of patients is associated with significant morbidity and mortality (Mesa*, et al* 2006).

Spleen's irradiation is also employed to reduce symptoms secondary to splenomegaly, but symptomatic improvement is variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted. Usual treatment consisted in supportive care, myelotoxic drugs in cases of myeloproliferation.

D. Treatment with RUXOLITINIB

INCB018424 phosphate, designated RUXOLITINIB throughout, is a novel, potent, reversible and selective inhibitor of JAK1- and JAK2-STAT signaling (Quintas-Cardama, *et al*) that is currently under development for treatment of myeloproliferative neoplasia (MPN) and advanced hematologic malignancies.

1. Preclinical studies

RUXOLITINIB inhibited the splenomegaly and morbidity/mortality in mice resulting from intravenous inoculation of cells expressing the same mutated JAK2 (V617F) implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs. Effects of RUXOLITINIB that were seen in toxicology studies rats (repeated dosing for 6 months) and dogs (12 months) were mainly myelosuppressive and are believed to be associated with the mechanism of action of RUXOLITINIB (inhibitor of JAK-STAT signaling). Genetic toxicology assessments (evaluation of RUXOLITINIB in bacterial mutagenicity assay, in vitro chromosome aberration assay, and in vivo micronucleus assay) in rats were negative. In safety pharmacology evaluations, an adverse decrease in minute volume in a respiratory study in female rats was noted only at the highest dose. In a cardiovascular evaluation of RUXOLITINIB in dogs, electrocardiogram (ECG) parameters and ventricular repolarization were unaffected at all doses, whereas the compound lowered blood pressure and increased heart rate compared to vehicle control at the highest dose evaluated. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. RUXOLITINIB was not teratogenic in either rat or rabbit. No effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses.

More detailed information on pharmacology of RUXOLITINIB, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the Investigator Brochure (IB).

2. Clinical pharmacology of RUXOLITINIB

Following oral, single-dose administration of RUXOLITINIB capsules in the fasted state, RUXOLITINIB was absorbed rapidly, typically attaining peak plasma concentrations within 1 to 3 hours after administration for all doses (Shi*, et al*). After attaining C_{max}, the RUXOLITINIB plasma concentrations declined with a mean terminal-phase disposition $t_{1/2}$ of approximately 3-5 hours. The mean RUXOLITINIB C_{max} and AUC increased with approximately linear proportionality to dose for the entire dose range evaluated of 5 to 200 mg. There was no significant food effect on absorption or exposure. The double-blind, randomized, placebo-controlled, single dose escalation study [INCB 18424-131] was conducted to investigate the food effect. T_{max}, C_{max}, AUC in particular were determined. The main conclusion was that overall magnitude of the food effect on the RUXOLITINIB exposure is not expected to be clinically significant.

RUXOLITINIB is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. Systemic exposure of RUXOLITINIB was appreciably increased (AUC 2-fold higher) when given in combination with ketoconazole, a potent CYP3A4 inhibitor, with a similar effect observed on the pharmacodynamic (PD) activity (cytokine-induced STAT3 phosphorylation) (Shi*, et al*, Shilling*, et al*). CYP3A4 inducers significantly decreased the exposure to RUXOLITINIB, with essentially no difference observed on the PD activity (cytokine-induced STAT3 phosphorylation). This suggests that CYP3A4 induction with rifampin results in metabolism of RUXOLITINIB to active metabolites which also inhibit JAKs (Shi*, et al*). A list of inhibitors or inducer of CYP3A4 is available in **Annexe 2**.

RUXOLITINIB was given as a single 25 mg dose to patients with varying degrees of renal function, [INCB 18424-142] study, and to patients with varying degrees of hepatic dysfunction or with normal hepatic function, [INCB 18424-137] study. Mild, moderate or severe impairment of renal function had no statistically significant effect on PK or PD parameters; patients requiring dialysis showed prolonged PD activity without a demonstrable effect on RUXOLITINIB clearance. In patients with mild, moderate and severe hepatic impairment, the mean total AUCs of RUXOLITINIB were 88%, 29% and 66% higher, respectively, compared to patients with normal hepatic function. Terminal half-life of RUXOLITINIB was increased in patients with hepatic impairment by approximately 2-fold compared to healthy controls. The patients with severe hepatic impairment showed modestly protracted PD activity compared to the other hepatically impaired patients who displayed PD activity similar to the healthy controls.

Additional details as to the clinical pharmacology of RUXOLITINIB may be found in the IB.

3. RUXOLITINIB clinical safety in healthy volunteers

RUXOLITINIB has been administered in single or multiple doses to over 200 healthy volunteers. In single dose studies, RUXOLITINIB has a well established safety profile and has been well tolerated with Adverse Events (AEs) generally mild in intensity, reversible and of similar incidence following RUXOLITINIB treatment compared with placebo or with other control treatments.

In a 10-day multiple dose study, a total of 71 healthy volunteers in 6 cohorts received doses of 50 mg qd, 100 mg qd, 15 mg b.i.d., 25 mg b.i.d. or 50 mg b.i.d. RUXOLITINIB or placebo, [INCB 18424-132] study (Shi*, et al*). RUXOLITINIB was well tolerated in the study, with most AEs reported equally by both RUXOLITINIB-treated and placebo-treated volunteers. Neutropenia was noted in 3 volunteers receiving the highest dose of RUXOLITINIB, 50 mg b.i.d. Neutropenia at the Grade 4 level led to study drug discontinuation on Day 5 in one volunteer and was reported as a Serious Adverse Event (SAE). There was a decline in mean absolute neutrophil count (ANC) and, to a lesser extent, in mean WBC count values with RUXOLITINIB doses of 15 mg b.i.d. or higher. In general ANC or WBC returned to Baseline levels within 1 to 2 days following the last dose of study drug. Doses of 25 mg b.i.d. and 100 mg qd were determined to be the maximum tolerated doses (MTDs) in this study based on the dose limiting toxicity (DLT) of neutropenia.

A definitive QT study was carried out in 50 healthy volunteers, evaluating the effects of single doses of 25 mg or 200 mg RUXOLITINIB compared with placebo and 400 mg moxifloxacin (positive control). The overall conclusion was that there appeared to be no adverse impact on ECG signaling (little change in heart rate, QRS duration, QTcF interval, and a slight, non-clinically significant, increase in PR interval) with the administration of RUXOLITINIB.

For additional details related to studies conducted in healthy volunteers, consult the IB.

4. RUXOLITINIB clinical safety in and efficacy in myelofribosis patients (Phase I/II study)

Study [INCB 18424-251] is an ongoing Phase I/II open label study of RUXOLITINIB in patients with PMF, PPV-MF or PET-MF in patients with baseline platelet counts of at least 100 G/L (Verstovsek*, et al* 2010). A total of 154 patients have been enrolled and treated at twice daily dose regimens of 10 mg b.i.d. to 50 mg b.i.d., or once daily regimens of 25 mg qd to 200 mg qd. Patients enrolled since August 2008 have had individually titrated dose regimens that begin at doses of 10 mg b.i.d., for patients with baseline platelets 100 G/L - 200 G/L, or 15 mg b.i.d., for patients with baseline platelets > 200 G/L, with intra-patient dose escalation allowed up to doses of 20 mg b.i.d. or 25 mg b.i.d., respectively.

Efficacy data from this study demonstrate marked and durable reductions in spleen size which has been measured as palpable length below the left costal margin. Twice daily regimens were associated with a prompt decrease in spleen size; the reduction in spleen length appears dose-dependent. The effect on decreasing spleen size was still evident after many months of continued dosing. Once daily dosing regimens also are associated with an initial, rapid decline in spleen size and show approximate dose dependence. Spleen reduction occurred regardless of presence/absence of the *JAK2*V617F mutation and independent of the MF disease subtype (PMF, post-PV MF or post-ET MF) (Verstovsek*, et al* 2010).

Progressive myeloproliferative neoplasms are associated with weight loss and cachexia, presumably due to deregulation and abnormal elevation of a variety of pro-inflammatory cytokines.

In the [INCB 18424-251] study, after an initial weight loss (presumably due to the rapid decrease in splenomegaly and hepatomegaly and loss of ascites and/or pleural effusions) there was a gain in total body weight that was somewhat dose-dependent. Weight gains were present in most patients, importantly, including those with Body Mass Index (BMI) at baseline in the lowest quartile (BMI below ~ 22).

A prompt shift in the Eastern Cooperative Oncology Group (ECOG, **Annexe 3**) performance scores in individuals with scores of 1 or 2 towards a score of 0 was noted in this study and this improvement was maintained over 24 months.

The Modified Myelofibrosis Symptom Assessment Form (MFSAF, **annexe 4**) developed by Mesa et al, and based on an international internet-based survey of over 1000 patients with myeloproliferative diseases (Mesa*, et al* 2011) was used to probe a range of constitutional symptoms that are related to splenomegaly (including impaired ability to ambulate, abdominal pain and discomfort and early satiety) and elevated cytokines (including fatigue, night sweats and pruritus). Between 45% and 94% of patients in study [INCB 18424-251] reported a given symptom at baseline. After 2 or more weeks of RUXOLITINIB therapy, 28% to 61% of patients showed a reduction in individual symptom scores of at least 50% after 6 cycles of therapy when all doses were combined and assessed together.

In summary, RUXOLITINIB was associated with prompt and marked reduction in spleen size, gains in total body weight, improvement in ECOG status performance scores and improvement in constitutional symptoms that can be debilitating in this patient population. Refer to the IB for more complete information.

RUXOLITINIB has been well tolerated by this aged population with advanced disease. Most adverse events were mild to moderate in severity, considered unrelated to study drug administration and not dose dependent. Related adverse events occurring in at least 8 patients (5%) included in the safety database through December 31, 2009 were restricted to thrombocytopenia (66 patients, 43%), anemia (45 patients, 29%), weight increased (11 patients, 7%), diarrhea (10 patients, 6.5%) and fatigue (8 patients, 5%).

Both anemia and thrombocytopenia represent JAK2-inhibitor myelosuppression, and are therefore not unexpected for a JAK2 inhibitor. Thrombocytopenia represents the DLT in the population of the [INCB 18424-251] study. Forty (40) patients (26% of study population) had a grade 3 or grade 4 decline in platelet (PLT) count during the study (31 grade 3 events, 9 grade 4 events). Patients with grade 3 or grade 4 thrombocytopenia entered the study, in general, with PLT counts less than 200 G/L, although there are exceptions to this trend. Thrombocytopenia occurred rapidly: 20% of grade ≥ 3 events occurred in the first 4 weeks of dosing, just under half (48%) of grade ≥ 3 events occurred in the first 16 weeks of dosing. The decrease in PLT counts (expressed as median percent change from baseline) occurred almost entirely over the first 4 weeks, with additional gradual decline afterwards.

Recently, a "RUXOLITINIB withdrawal syndrome" has been reported by Tefferi et al from the Mayo Clinic Study (Tefferi and Pardanani 2011) consisting in an acceleration of the disease with acute enlargement of the spleen, worsening cytopenias or sepsis like syndrome occurring several days after ruxolitinib discontinuation.

5. Phase III studies for ruxolitinib

Two randomized Phase 3 studies (COMFORT 1 and COMFORT 2) were conducted in patients with myelofibrosis (either primary myelofibrosis, post-polycythemia Vera myelofibrosis or post-essential thrombocythemia-myelofibrosis) (Harrison, *et al* 2012, Verstovsek, *et al* 2012). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the IWG Consensus Criteria.

The starting dose of RUXOLITINIB was based on platelet count. Patients with a platelet count between 100 and 200 G/L were started on RUXOLITINIB 15 mg twice daily and patients with a platelet count greater than 200 G/L were started on RUXOLITINIB 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily for patients with platelet counts between 100 to less than or equal to 125 G/L, of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 G/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 G/L.

Study COMFORT 1 (Verstovsek, *et al* 2012)

COMFORT 1 was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The median age was 68 years (range 40 to 91 years) with 61% of patients older than 65 years and 54% were male. Fifty percent (50%) of patients had primary myelofibrosis, 31% had post-polycythemia Vera myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis. Twenty-one percent (21%) of patients had red blood cell transfusions within 8 weeks of enrolment in the study. The median hemoglobin count was 105 g/L and the median platelet count was 251 G/L. Patients had a median palpable spleen length of 16 cm below the costal margin, with 81% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) of 2595 cm^3 (range 478 cm^3 to 8881 cm^3). Patients were treated with RUXOLITINIB or matching placebo. The primary efficacy endpoint was the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT. Secondary endpoints included duration of a 35% or greater reduction in spleen volume, proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary and overall survival.

Study COMFORT 2 (Harrison, *et al* 2012)

COMFORT 2 was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to RUXOLITINIB versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, the medications received by more than 10% of patients were hydroxyurea (47%) and glucocorticoids (16%). The median age was 66 years (range 35 to 85 years) with 52% of patients older than 65 years and 57% were male. Fifty-three percent (53%) of patients had primary myelofibrosis, 31% had post-polycythemia Vera myelofibrosis and 16% had post-essential thrombocythemia myelofibrosis. Twenty-one percent (21%) of patients had red blood cell transfusions within 8 weeks of enrolment in the study. The median hemoglobin count was 104 g/L and the median platelet count was 236 G/L. Patients had a median palpable spleen length of 15 cm below the costal margin, with 70% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by MRI or CT of 2381 cm^3 (range 451 cm^3 to 7765 cm^3).

The primary efficacy endpoint was the proportion of patients achieving 35% or greater reduction from baseline in spleen volume at Week 48 as measured by MRI or CT. A secondary endpoint in Study 2 was the proportion of patients achieving a 35% or greater reduction of spleen volume as measured by MRI or CT from baseline to Week 24.

COMFORT 1 and 2 studies Efficacy Results

Efficacy analyses of the primary endpoint in COMFORT 1 and 2 Studies are presented in **Table 3** below. A significantly larger proportion of patients in the RUXOLITINIB group achieved a 35% or greater reduction in spleen volume from baseline in both studies compared to placebo in Study 1 and best available therapy in Study 2. A similar proportion of patients in the RUXOLITINIB group achieved a 50% or greater reduction in palpable spleen length.

Table 3. Percent of patients with 35% or greater reduction from baseline in spleen volume at week 24 in study 1 and at week 48 in study 2 (intent to treat)

	COMFORT 1		COMFORT 2	
Time Points	Week 24		Week 48	
	RUXOLITINIG (N=155)	Placebo (N=154)	RUXOLITINIB (N=146)	Best Available Therapy (N=73)
Number (%) of Patients with Spleen Volume Reduction by 35% or More	65 (41.9)	1 (0.7)	41 (28.5)	0
P-value	< 0.0001		< 0.0001	

In COMFORT 1 study, myelofibrosis symptoms were a secondary endpoint and were measured using the modified MFSAF v2.0 diary. The modified MFSAF is a daily diary capturing the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms “absent” and 10 representing “worst imaginable” symptoms. These scores were added to create the daily total score, which has a maximum of 60.

Table 4 presents assessments of Total Symptom Score from baseline to Week 24 in Study 1 including the proportion of patients with at least a 50% reduction (ie, improvement in symptoms). At baseline, the mean Total Symptom Score was 18.0 in the RUXOLITINIB group and 16.5 in the placebo group. A higher proportion of patients in the RUXOLITINIB group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of less than 4 weeks.

Table 4. Improvement in Total Symptom score

	RUXOLITINIB (N=148)	PLACEBO (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
P-value	< 0.0001	

In COMFORT 1 study, a survival analysis based on a planned data cutoff with 4 additional months of follow-up revealed a significant advantage for patients treated by RUXOLITINIB (8.4% versus 15.6% mortality rate ; hazard ratio, 0.50; 95% CI, 0.25 to 0.98; P = 0.04) at the time of data cutoff).
In COMFORT 2 study, no advantage for overall survival or leukemia free survival was detected. A 12 months, 124/146 patients treated by RUXOLITINIB and 50/73 patients treated by placebo were alive (median survival not reached).

E. Transplantation for patients with myelofibrosis

1. Myeloablative conditioning regimen (MAC)

For a subset of patients who are younger, allogeneic stem cell transplantation is the only curative option for these patients. In the ninety's, first great series were published to report substantial cure after allogeneic hematopoietic stem cell transplant (HSCT). Because of the fibrosis of the bone marrow in this disease, many specialists believed that engraftment after HSCT would not be possible in patients with myelofibrosis. In fact, engraftment after myeloablative conditioning regimen has been progressively demonstrated, ranging from 70 to 90%, a little bit lower than after other hematological malignancies.

Engraftment has been reported better after peripheral blood stem cell (PB) as source of stem cells, higher nucleated cells infused from the graft and if the patient has no splenomegaly before transplantation (Deeg, *et al* 2003, Guardiola, *et al* 1999). Myelofibrosis can persist several weeks or months after HSCT and a minimum delay of 6 months after HSCT is required to observe bone marrow normalization in the recipient (disappearance of myelofibrosis). Guardiola et al reported a "plateau" (54%) for overall survival (OS) after HSCT in patients who benefit from a HSCT from an HLA-matched related donor. Several risk factors for survival have been reported included disease stage (Lille score, peripheral blasts, stage of fibrosis, ctygenetics), age, comorbidity score (Deeg, *et al* 2003, Guardiola, *et al* 1999, Kerbauy, *et al* 2007).

2. Non myeloablative conditioning regimen

At the beginning of the 2000's, less toxic conditioning regimen have been developed in order to transplant older patients who could not benefit from HSCT preceded from a myeloablative conditioning regimen because of risk of toxicity and mortality related to the procedure, particularly the graft-versus-host disease (GVHD) leading to significant non-relapse mortality (NRM). In the study published by Guardiola et al, patients who were older than 45 years had survival less than 15%, which can be considered as a non acceptable strategy for these patients (comparing to a 60% OS in younger patients). As median age at myelofibrosis diagnosis is 60 to 65 years, very few patients with myelofibrosis could benefit from a standard HSCT. Again, the fear of poor hematological recovery and the risk of graft failure emerge when first non MAC were applied. Devine et al reported the first patients with myelofibrosis older than 45 years prospectively included in a reduced intensity conditioning regimen (RIC) protocol associating Fludarabine plus Melphalan 140mg/m² (Devine, *et al* 2002). All four patients engrafted and no mortality was deplored. Several other studies reported high engraftment rate and OS > 60% (Rondelli, *et al* 2005). Kroger et al reported a large prospective study using a RIC consisted in Fludarabine plus Busulfan confirming high engraftment rate and OS (Kroger, *et al* 2009). Non-relapse mortality was 30%. The French cohort of transplanted patients has been recently published. Most patients received a RIC and engraftment rate was > 80% with a median OS after HSCT at 21 months (Robin, *et al*). Results of main studies are shown in **Table 5**. Risk factors for OS after HSCT preceded by RIC are quite similar as those after MAC: age, comorbidity score (**Annexe 5**), Lille score, disease status but also spleen size before transplantation.

Table 5. Main studies reported results of HSCT for patients with myelofibrosis

N	Median age in years	Lille Int- or high risk disease	Splenectomy before HSCT	NRM (years)	OS (years)
55[1]	42	76%	49%	27% (1 y)	47% (5 y)
56[2]	43	53%	36%	32% (3 y)	58% (3 y)
104[3]	49	58%	38%	ND	61% (5 y)
100[4]	49	90%	38%	43% (3 y)	42% (3 y)
103[5]	55	83%	14%	16% (1y)	67% (5 y)
289[6]	46	64%	24%	35-50% (5 y)	37% (5 y)
147[7]	53	83%	40%	29% (4 y)	39% (4 y)
170[8]	51	88%	18%	74% (1 y)	26% (1 y)

1-8: references of the studies (chronological order) from 1999 to 2011. 1: (Guardiola, *et al* 1999), 2: (Deeg, *et al* 2003), 3: (Kerbauy, *et al* 2007), 4: (Patriarca, *et al* 2008), 5: (Kroger, *et al* 2009), 6: (Ballen, *et al* 2010), 7: (Robin, *et al* 2011), 8: (Scott, *et al* 2012)

3. Role of the spleen during the HSCT

As already discussed, splenomegaly in patients with MF has a major impact on engraftment l (Bacigalupo, *et al* 2010, Kroger, *et al* 2009, Robin, *et al*, Rondelli, *et al* 2005). In at least 3 studies, large splenomegaly before transplantation is a risk factor for poor outcome after HSCT. In the French study from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC), to improve engraftment and general outcome after HSCT, splenectomy has been performed in 40% of cases (**Table 5**) and was a predictor for better OS in multiple analysis.

Table 6. Risk factors for OS in the French cohort of transplanted patients

Variable	Hazard Ratio	95% CI	P value
Male without splenectomy	3.45	2.07 to 5.77	<0.0001
Non-HLA identical sibling donor	1.86	1.12 to 3.07	0.016
Non chronic phase disease (blasts > 20%)	1.81	1.02 to 3.21	0.043

An increased risk of relapse after HSCT has been suggested by the Kroger study but in this study, very few patients were splenectomized (14%) and splenectomy was possibly limited to patients with the most progressive disease. Splenectomy was not a poor risk factor in multivariate analysis (Kroger, *et al* 2009).

In the Scott et al study, patients who undergone splenectomy before transplantation had a lower post-HSCT mortality after adjusting for disease stage (Scott, *et al* 2012).

Unfortunately, splenectomy in MF patients is at risk for postsurgical complications as hemorrhage and thrombosis and the risk of death exists also (Mesa, *et al* 2006). A systematic splenectomy for MF patients planned to HSCT cannot be recommended. Only patients with very large spleen should be splenectomized in the absence of surgical contraindication. We also reported 2 patients with splenomegaly who had a contraindication to surgery before HSCT and could not be splenectomized. Three months after HSCT, a poor hematological reconstitution was observed and patients continued to require a lot of blood transfusion. A splenectomy after HSCT was performed and hematological parameters rapidly recovered (Robin, *et al* 2010). In fact, this surgery is not always realizable because of poor general conditions of transplanted patients.

4. JAK2 mutation in the context of transplantation

Controversial studies exist concerning the prognostic impact of JAK2 mutation in patients with myelofibrosis undergoing HSCT. Two German studies conclude to better outcome of patients with JAK2V617F mutation (Alchalby, *et al* 2010, Alchalby, *et al* 2012) whereas a more recent study from Seattle does not (Scott, *et al* 2012).
After HSCT, JAK2 allele burden surveillance has been shown to be a reliable molecular disease marker able to predict the relapse. Its monitoring after HSCT can be useful to manage immunosuppression in patients without GVHD (Alchalby, *et al* 2010).

5. Rational and potential benefit for the use of RUXOLITINIB before HSCT

HSCT remains the only curative option for MF patients but NRM is relatively high including after RIC, ranging from 10 to 40%. The NRM depends from patients and disease characteristics, conditioning regimen, type of donor, immunological and / or infectious events occurring after HSCT. Splenomegaly in patients with myelofibrosis has also a negative impact on survival. Relapse rate ranges from 10 to 30%. Some efforts should be made in order to decrease the NRM and relapse rate.
Ruxolitinib has been reported to be safe in patients with myelofibrosis reducing general symptoms and spleen size in the majority of patients as well as proinflammatory cytokines (Harrison, *et al* 2012, Verstovsek, *et al* 2010, Verstovsek, *et al* 2012). Our hypothesis is that RUXOLITINIB at 15 mg twice daily starting dose, as established by the dose-escalation study (Verstovsek, *et al* 2010), has the potential to reduce NRM and relapse rate after HSCT through the following action:

- Improvement of general performance status before transplantation
- Decrease of the co-morbidity score pre-transplantation
- -Decrease of the prognostic scores including general symptoms as the IPSS
- -Reduction of spleen size
- -Limitation of splenectomy in patients scheduled for transplantation, limiting consequently postoperative comorbidities as hemorrhage and thrombosis and increasing engraftment because of reduced spleen size in all patients
- -Possible less toxicity and less GVHD related to less pro-inflammatory cytokines in circulation

- -Less relapse due to a better control of the disease before HSCT
- -More patients with donor able to undergo transplantation (less contraindication related to performance status or disease evolution).

The primary aim of the present study is to test the advantage on post HSCT disease-free survival (DFS) in young patients (< 70 years) who received JAK2 inhibitors before HSCT.

6. Potential risk of RUXOLITINIB before HSCT

The primary clinical risks with RUXOLITINIB treatment are the potential sequelae of decreased thrombopoiesis and to a much lesser extent hemopoiesis and myelopoiesis, most probably the result of *JAK2* dependent signaling which is inhibited by RUXOLITINIB. Dose-dependent, reversible thrombocytopenia is observed with RUXOLITINIB and is its primary adverse effect, but only two cases of mild epistaxis in a thrombocytopenic patient considered possibly related to RUXOLITINIB have occurred in approximately 150 treated subjects. For a significant population of thrombocytopenic MF patients, a previous phase I/II study(Verstovsek, *et al* 2010), has established thrombocytopenia as the DLT of RUXOLITINIB in MF patients with a MTD of both 25 mg b.i.d. and 100 mg qd. The incidence of grade ≥ 3 thrombocytopenia in this phase I/II trial was 20% at 10 mg b.i.d., 2.9% at 15 mg b.i.d. and 36% at 25 mg b.i.d. The higher incidence of grade ≥ 3 thrombocytopenia in the 10 mg b.i.d. dose group compared to 15 mg b.i.d. one can be partially explained by the more frequent presence of patients with low baseline PLT counts in the former dose group compared to the latter one.

Data from the same trial show that patients who entered the study with baseline PLT counts 100-150 G/L developed grade ≥ 2 thrombocytopenia more frequently (75% vs. 37%, respectively, for the most commonly used doses that will be relevant to this trial, 10 mg b.i.d. and 15 mg b.i.d.) compared with patients with baseline PLT counts > 150 G/L, although with a similar nadir (grade 2 and 3). Thrombocytopenia occurred rapidly, and resolved with drug interruptions or dose decreases (Verstovsek, *et al* 2010). Thus, while JAK inhibition is clearly, and not unexpectedly, associated with decreasing platelet counts, emergent thrombocytopenia can be managed with dose decreases or brief drug interruptions.

An ongoing study currently test the feasibility of RUXOLITINIB in patients with thrombocytopenia < 100 G/L in patients with primary or secondary myelofibrosis (Clinical Study Protocol INC424A2201). A theoretical risk of neutropenia exists with RUXOLITINIB treatment, although only a few examples of Grade 3 or 4 neutropenia have been observed in MF patients in the previous open-label study, generally in subjects who entered the study with baseline ANC levels near the lower limit of laboratory normal.

Worsening of anemia has been seen in some patients. No cases of opportunistic infections have been observed. A few subjects have had an apparent worsening of their pre-study constitutional symptoms following rapid cessation of RUXOLITINIB and a gradual tapering of RUXOLITINIB and use of steroids in fragile subjects may be prudent when stopping RUXOLITINIB(Tefferi and Pardanani 2011). Additional information is available in the IB. These risks will be managed in the current study by using platelet and neutrophil counts for baseline stratification of starting dose and in-study dose adjustments.

The use of RUXOLITINIB before HSCT can also have negative impact for HSCT outcome and engraftment, GVHD, toxicity, infections rate and survival will be carefully monitoring.

7. Justification of route, dose and duration of treatment

RUXOLITINIB is administered orally. In the dose-escalation study for RUXOLITINIB, including patients with myelofibrosis, BID dose regimens from 10 mg BID to 50 mg BID have been examined (Verstovsek*, et al* 2010). With 15 mg BID, spleen size reduction was quite similar to this observed with 25 mg BID and grade 3-4 thrombocytopenia was significantly lower (null in patients enrolled with PLT > 100 G/L) as seen in **Table 7**. Positive effects of RUXOLITINIB appear rapidly after initiation and >80% of responders have already a response at 1 month. According to previous studies, a total duration of pre-HSCT RUXOLITINIB of 4 months is appropriate, and notably all responders should have respond at this date.

Table 7. Reduction of spleen size and incidence of thrombocytopenia in the Study INCB 18424-251 (Verstovsek, *et al* 2010)

Reduction of Palpated Spleen Size and Incidence of Thrombocytopenia in Study INCB 18424-251 Parameter	25 mg BID	15 mg BID	10 mg BID
N as of February 1, 2009	47	34	29
Proportion achieving at least 50% reduction in spleen size	56% (22 of 39)	54% (15 of 28)	33% (8 of 24)
Proportion with Grade 3 thrombocytopenia	23.4%	0%	3.4%
Proportion with Grade 4 thrombocytopenia	6.4%	0%	0%

III. Study objectives

A. Primary objective

The primary objective is to observe a 12-month postHSCT disease-free survival (DFS) higher than 50%.

B. Secondary objectives

1. Patients who received a HSCT

Rate of patients with donor who will be transplanted

Reduction of splenectomy rate (expected at 40%) before transplantation

No increase in HSCT comorbidity score from inclusion to transplantation

Improvement of QOL from inclusion to date of transplantation

Reduction of acute GVHD incidence and chronic GVHD

Improvement of engraftment rate

Reduction of relapse rate

Reduction of NRM

Improvement of OS

2. All patients

Reduction of spleen size
Improvement of performance status
Reduction of general symptom related to MF (MFSAF)
Comparison of hematological response (complete and partial) in patients with and without donor
Comparison of transfusion dependence (RBC or PLT transfusions) in patients with and without donor
Comparison of OS in patients with and without donor
Comparison of QOL in patients with and without donor
Severe infection incidence

IV. Definitions of endpoints

A. Primary endpoint

DFS is defined as the probability to be alive and in remission (see statistical method)

B. Secondary endpoints

1. Hematological response

Criteria for response are defined according to IWG consensus criteria (Tefferi, *et al* 2006) ANNEXE 17.
In order to avoid unnecessary invasive bone marrow biopsy during the protocol, this procedure should not be repeated if hematological conditions do not change over time.

2. Transfusion independency

The transfusion RBC or PLT independency is defined as the first day of 60 consecutive days during which patients do not require RBC or PLT transfusion.

3. Spleen size

Spleen size will be assessed by palpation, or any imagery at registration and by tomography scan before transplantation (60 to 30 days before conditioning regimen for transplantation).

4. Mortality

All deaths occurring during the study are prospectively collected (SAE)

5. Relapse

Relapse can be considered only in patients who had been considered in CR before. Reappearance of any sign of the disease (clinical, blood) should be completed by a bone marrow analysis in order to define the disease recurrence.

6. Transformation into acute leukemia

Patients who have more than 20% of blasts in blood or in bone marrow will be considered as transformed into acute leukemia. If a transformation is suspected, a bone marrow aspiration or biopsy is preferable.

7. Performance status

Performance status will be evaluated by ECOG scale (**Annexe 3**).

8. General symptoms related to MF

General symptoms related to MF will be assessed by a specific questionnaire (**Annexe 4**).

9. Comorbidity index

Co-morbidity index will be defined by Sorror et al (Sorror*, et al* 2005). It will be calculated at registration and 4 months after registration (before transplantation and after an eventual splenectomy). All variables required to calculate this index are listed in **Annexe 5**.

10. Acute and chronic GVHD incidence

GVHD concerns only patients who received an allogeneic transplantation.
Acute GVHD will be assessed until day 200 postHSCT and graded according to Glucksberg modified scale (Glucksberg, *et al* 1974) (**Annexe 6**).
Chronic GVHD will be assessed according to Shulman (Shulman, *et al* 1980) (**Annexe 7**).

11. Engraftment after HSCT

ANC engraftment after HSCT is defined as the first of 3 consecutive days of ANC > 0.5 G/L.
PLT engraftment after HSCT is defined as the first of 7 consecutive days of PLT count > 20 G/L.

12. Infections

Infections will be defined according to EBMT criteria (Cordonnier, www.ebmt.org) including EORTC definitions for fungal infections (Ascioglu, *et al* 2002) (**Annexe 8**). Only infections requiring a curative treatment will be considered in this study excluding asymptomatic viral reactivation or asymptomatic catheter bacteriemia or benign infection. Details on infections considered for this study are given in **Annexe 9 and 10**. Infection monitoring **will stop at 3 months post transplantation** (7months for non-transplanted patients).

13. Quality of live

The version EORCT questionnaire will be used (**Annexe 11**) available on **http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_c30.pdf**.

14. JAK2 status mutation and allele burden

JAK2V617F mutation status and allele quantification will be performed at registration, 3 months after inclusion/before transplantation, 7 months after inclusion/3 months postHSCT and 16 months after inclusion/12 months postHSCT in Saint-Louis Hospital, laboratoire de biologie cellulaire (**Annexe 12**).

MPL mutation status will be checked at registration in Saint-Louis Hospital, laboratoire de biologie cellulaire. Method and the specific form are shown in **Annexe 12 and 13**.

15. Cytokine measure and immunological analysis

Blood samples for cytokine measure and immunological analysis will be collected at the same time and sent to the same laboratory (Hôpital Saint-Louis) than samples for JAK2 mutation research (**Annexe 12 et 13**).

Cytokines measured are:

human IL-1b, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40 Dp70), IL-13, IL-15, IL-17, TNF-a, IFN-a, IFN-g, GM-CSF, MIP-1a, MIP-1b, IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-CSF, EGF, FGF-basic, GROb, MMP–3, MMP–13, MMP–9, TGFb, PDGF, VEGF et platelet factor 4HGF.

On bloods cells, circulating CD34+ cells and CD45+ cells will be analyzed for the expression of CD14, CD15, CD19, CD56, CD38lo, Thy1+, cKit+ to define the representation of each phenotype. The presence of lymphoid committed progenitors will be tested by CD34+ CD2+ also B cell precursors by the expression of CD5+.

16. Biological collection

Serum and blood cells samples remaining from the biological analysis will be cryopreserved according to good clinical practice in Hôpital Saint-Louis, Laboratoire de biologie cellulaire, 1 avenue Claude Vellefaux, 75010 Paris.

17. Blood chimerism

Blood chimerism will be performed in each transplantation centre according to local method. The sensibility will not be < 95% and chimerism and chimerism should be performed on total cells blood and on CD3+ sorted cells blood.

18. Summary of endpoints and diary

Variables	Time of endpoints
MF-SAF	D1, M1, M2, M3, M7, M10, M16, M20, M24
Pregraft comorbidity index	D1 and M3
Performance status	D1, M1, M2, M3, M7, M10, M16, M20, M24
Quality of life	D1, M3, M7, M16 and M24
Infection	D1, M3, M7
Haematological response	D1, D15, M1, M2, M3, M4, M5, M7, M10, M16, M20, M24
JAK2 status mutation (V617 or MPL)	D1
JAK2 status mutation and allele burden in patients positive at registration	M3, M7, M16
Cytokine measure and immunological analysis and biological collection (Hôpital Saint-Louis)	D1, M3, M7, M16
Transfusion independency	D1, M1, M2, M3, M7, M16, M20, M24
Spleen size	D1, M1, M2, M3, M5, M7, M10, M16, M20, M24
Acute GVHD*	M7, M10 (M3 and M6 post transplantation)
Engraftment after HSCT*	M7 (M3 post transplantation)
Chronic GVHD*	M7, M16, M20, M24 (M3, M12, M16, M20 post transplantation)

*only for transplanted patients

V. Population

A. Inclusion criteria

Related to the patient

- Age between 18 and 69 years
- No comorbidity contraindicating the transplantation (see exclusion criteria)

Related to the disease

1. Primary or secondary myelofibrosis according to WHO definition (Barosi, *et al* 2008, Tefferi, *et al* 2007, Vardiman, *et al* 2009) **Annexe 1**

- Splenomegaly > 15 cm on imagery or palpable

- **<u>One criterion among:</u>**

-hemoglobin < 100 gr/L

-leucocytes < 4 G/L or > 25 G/L

-peripheral blood or bone marrow blasts > 10%

-chromosome 5, 7 or 17 aberrations

- **<u>Or the two criteria together</u>:**

-general symptoms (Weight lost > 10% in less than 6 months, "specific" fever > 37.5°C or night swear)

-peripheral blood blasts > 1% observed at least 2 times

Justification for inclusion criteria related to the disease

Disease criteria have been chosen according to usual classifications. Patients should be at intermediate / high risk according to IPSS (Cervantes, *et al* 2009), dynamic IPSS (Passamonti, *et al* 2010) or Lille score (Dupriez, *et al* 1996, Morel, *et al*). WBC cut-off has been adapted at 25 G/L according to IPSS to simplify inclusion criteria (and not according to Lille score). One criteria for acceleration of the disease according to (Tam, *et al* 2009b) is sufficient to include the patient. Poor cytogenetics is also sufficient to include the patient ((Hussein, *et al*, Tam, *et al* 2009a)).

B. Exclusion criteria

Conditions related to the patient

Comorbidities contraindicating the HSCT:

-Severe respiratory failure defined as dyspnea stage > II (**Annexe 14**)

-Uncontrolled cardiac failure, EF < 40%

-Severe renal failure (creatinine clearance < 30 ml/min) or hemodyalasis

-Degenerative progressive neurological disease

-Very severe liver disease (Liver cirrhosis, bilirubin > 2 x ULN, or AST/ALT > 5 x ULN)

-ECOG score > 2 (**Annexe 3**)

-Comorbidity index > 3 (**Annexe 5**)

Patients not able to give informed consent for any reason

Conditions related to the disease

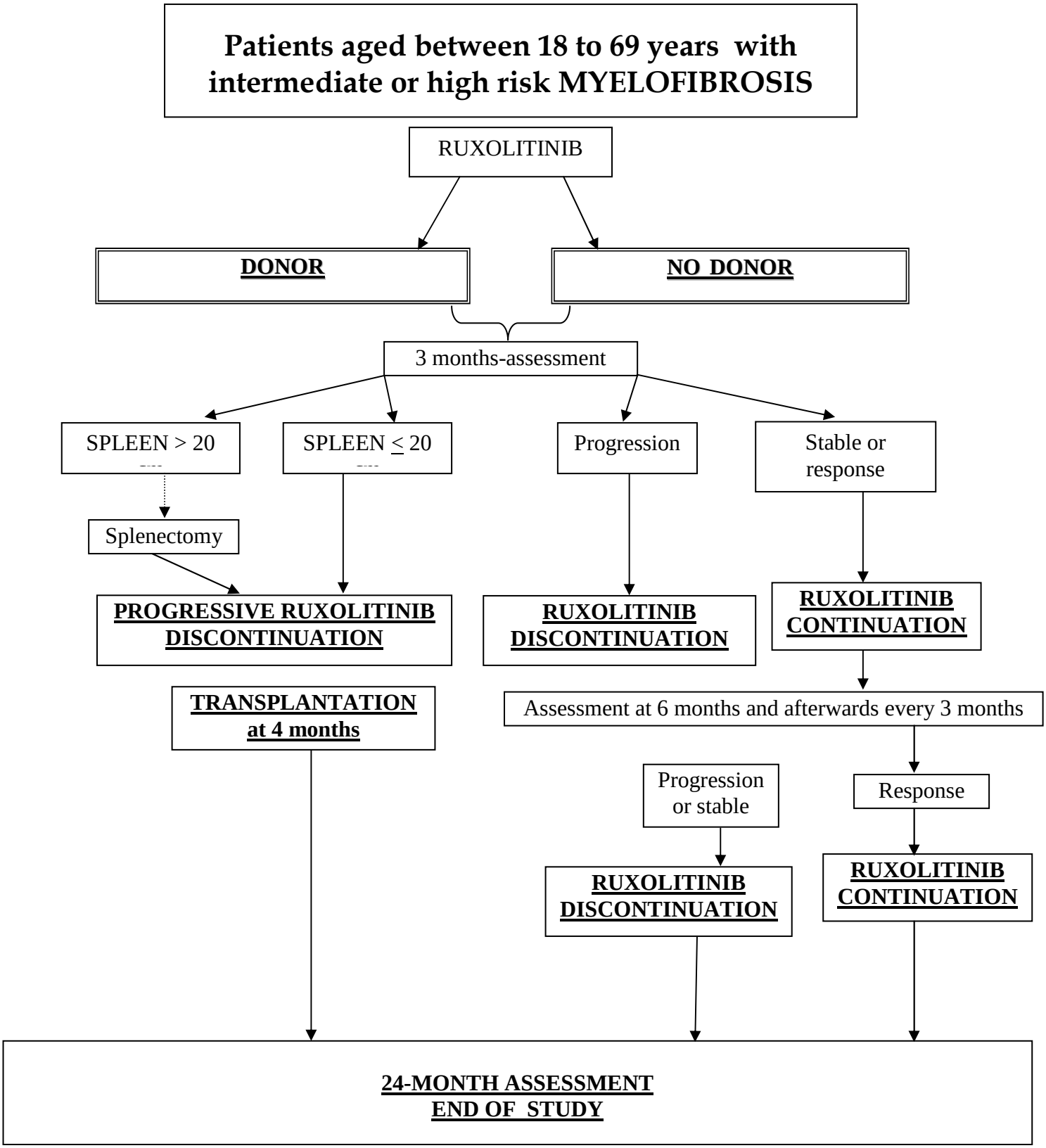
-Myelofibrosis transformed into acute leukemia defined as more than 20% blasts in peripheral blood or bone marrow observed at least 2 times in 4 weeks

-Previous treatment with JAK2 inhibitors

-Persistent thrombocytopenia < 50 G/L

VI. Trial design

A. Main phases of the study



B. Registration

On the day of registration the patient must meet all inclusion criteria and no exclusion criteria should be present.
Signed written consents will be obtained from the patient using forms approved by the CPP Paris VII.
Each centre should register its patients using the Registration Form for this study (**Annexe 15**) and fax it to GOELAMS office trials.
Contact: GOELAMS
Address: HOPITAL BRETONNEAU, 2 bd Tonnelé, 37044 TOURS CEDEX 1
Tel: (33)2 47 39 18 96
Fax: (33)2 47 37 35 12
A confirmation of registration will be send by Facsimile by the GOELAMS data manager to the site.

C. RUXOLITINIB treatment

1. Dosage and administration

1.1. Method of administration

RUXOLITINIB is dosed orally and can be administered with or without food.
If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

1.2. Initial Dose

Initial dose without P450 cytochrome inhibitor

1) Patients with PLT > 100 G/L:
- 15 mg BID

2) Patients with PLT < 100 G/L and > 50 G/L:
-10mg BID

Initial dose with strong P450 cytochrome inhibitor (list in Annexe 2)

1) Patients with PLT > 100 G/L:

- 7.5 mg BID (10 mg the morning and 5 mg the evening)

2) Patients with PLT < 100 G/L and > 50 G/L:

-5mg BID

1.3. Dose adaptation during treatment

1.3.1. Dose reduction Concomitant CYP3A4 Inhibitor Usage

A dose reduction of 50% for RUXOLITINIB is appropriate for subjects who take strong CYP3A4 inhibitors as concomitant medication (list of CYP P450 inhibitors on **Annexe 2)**. BID doses will be decreased by 50% follows in cases of strong CYP3A4 concomitant use (BID).

Potent inhibitors of CYP3A4 include oral ketoconazole, voriconazole, posaconazole, clarithromycin, itraconazole, nefazodone, telithromycin (Flockhart, et al 2007). Based on the very low overall bioavailability of topical ketoconazole, no dosage adjustment is needed for use with topical ketoconazole.

NOTE: once the course of therapy using a CYP 3A4 inhibitor has been completed, the subject should resume their prior BID dose regimen of RUXOLITINIB beginning the next day.

1.3.2. Dose adjustments according to hematological toxicity

- During the treatment, in cases of severe thrombocytopenia < 50 G/L or neutropenia < 0.5 G/L, ruxolitinib must be interrupted. After recovery of blood cell counts above this level, dosing may be restarted or increased following recovery of platelet counts to acceptable levels. **Table 8** illustrates the maximum allowable dose that may be used in restarting RUXOLITINIB after a previous interruption.

Table 8. Maximum restarting doses for ruxolitinib after safety interruption according to platelet count

	Maximum Dose When Restarting RUXOLITINIB Treatment *
Greater than or equal to 125 G/L	20 mg twice daily
100 to less than 125 G/L	15 mg twice daily
75 to less than 100 G/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 G/L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 G/L	Continue hold

- Dose reductions should be considered if the platelet counts decrease (but still > 50 G/L) as outlined in **Table 9** with the goal of avoiding dose interruptions for thrombocytopenia.

Table 9. Dosing recommendations for thrombocytopenia dose at time of platelet decline

Platelet Count	**25 mg twice daily**	**20 mg twice daily**	**15 mg twice daily**	**10 mg twice daily**	**5 mg twice daily**
	New Dose	**New Dose**	**New Dose**	**New Dose**	**New Dose**
100 to less than 125 G/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100 G/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75 G/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50 G/L	Hold	Hold	Hold	Hold	Hold

1.3.3. Dose adjustment according to haematological response

- Insufficient response

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.

Consider dose increases in patients who meet all of the following conditions (insufficient efficacy):

a. Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by CT or MRI;

b. Platelet count greater than 125 G/L at 4 weeks and platelet count never below 100 G/L;

c. ANC levels greater than 0.75 X G/L.

-No response or progression

Ruxolitinib will be stopped if the disease is uncontrolled:

-progression defined according to the IWG MRT (Tefferi, *et al* 2006)

1) leukemic transformation characterized by peripheral blood blasts > 20% for at least 4 weeks or bone marrow blasts > 20%

2) 50% increase spleen size as compared to baseline

-No hematological or clinical response 6 months after ruxolitinib treatment

1.4. RUXOLITINIB tapering

When RUXOLITINIB should be stopped before transplantation, RUXOLITINIB should be tapered per 5 mg every 3 days (**Table 10**). Corticosteroids (prednisolone) can be started in cases of inflammatory rebound (fever, more general symptoms, pains…) for 7 days or until improvement.

Table 10. Number of days required for RUXOLITINIB tapering according to the dosage in mg

	Tapering				
Initial dose	Dose from day 1 to day 3	Dose from day 4 to day 6	Dose from day 7 to day 9	Dose from day 10 to day 13	Day 14
25	20	15	10	5	STOP
20	15	10	5	STOP	
15	10	5	STOP		
10	5	STOP			
5	STOP				

Adjustment according organ impairment

Renal Impairment

In patients with moderate or severe renal failure (creatinine clearance < 60 mL/min but > 15mL/min), RUXOLITINIB dose should be decreased by 50%. RUXOLITINIB can be dialysed so no adaptation is required for patients on dialysis.

RUXOLITINIB should be avoided in patients with end stage renal disease (CrCl less than 15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment with platelet counts less than 100 G/L.

Hepatic Impairment

In cases of hepatic impairment, RUXOLITINIB should be decreased by 50%.

RUXOLITINIB should be avoided in patients with hepatic impairment with platelet counts less than 100 G/L.

2. Dispensation and accountability

Ruxolitinib will be supplied by Novartis France.

2.1. Nature and contents of container

The drug vial will contain 60 pills of Ruxolitinib.

2.2. Precaution of storage

Storage at room temperature

2.3 Compliance assement

The pharmacist of each center participating in the study must set up and update in real-time, a study drug tracking form, indicating:

- Patient's identification.
- Date and amount of Ruxolitinib delivered.

The investigator and the Pharmacist of every center shall never use study treatment units for patients not enrolled in the study.

2.4 Study treatment destruction

A written authorization must be given by the Sponsor prior to any destruction of study drugs. If immediate destruction of study drugs becomes mandatory for safety reasons, investigational centers may destroy study treatment units before a monitoring visit, provided traceability of study products is ensured through a study drug tracking form (including remaining products, documentation of dispatched, delivered and returned units).

3. Adverse reactions

Anemia

In the two Phase 3 clinical studies (Harrison*, et al* 2012, Verstovsek*, et al* 2012), median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (0.3%) discontinued treatment because of anemia. In patients receiving RUXOLITINIB, mean decreases in hemoglobin reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with RUXOLITINIB and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment (Verstovsek*, et al* 2012). Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with RUXOLITINIB and 1.7 in placebo treated patients.

Thrombocytopenia

In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks (Harrison*, et al* 2012, Verstovsek*, et al* 2012). Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 G/L was 14 days. Platelet transfusions were administered to 4.7% of patients receiving RUXOLITINIB and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving RUXOLITINIB and 0.9% of patients receiving control regimens. Patients with a platelet count of 100 G/L to 200 G/L before starting RUXOLITINIB had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 G/L (16.5% versus 7.2%).

Neutropenia

In the two Phase 3 clinical studies, 1.0% of patients reduced or stopped RUXOLITINIB because of neutropenia (Harrison, *et al* 2012, Verstovsek, *et al* 2012).

Table 11 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with RUXOLITINIB or placebo in the placebo-controlled study (Verstovsek, *et al* 2010).

Table 11. Severity of clinical hematology abnormalities

Laboratory Parameter	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Thrombocytopenia	69.7	9.0	3.9	30.5	1.3	0
Anemia	96.1	34.2	11.0	86.8	15.9	3.3
Neutropenia	18.7	5.2	1.9	4.0	0.7	1.3

Additional Data from the Placebo-controlled Study (Verstovsek, *et al* 2012)

25.2% of patients treated with RUXOLITINIB and 7.3% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 1.9% for RUXOLITINIB with 1.3% Grade 3 and no Grade 4 ALT elevations.

17.4% of patients treated with RUXOLITINIB and 6.0% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 0.6% for RUXOLITINIB with no Grade 3 or 4 AST elevations.

16.8% of patients treated with RUXOLITINIB and 0.7% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was 0.6% for RUXOLITINIB with no Grade 3 or 4 cholesterol elevations.

D. Splenectomy

One of secondary objective is to test a reduction in splenectomy rate in **patients planned to transplantation**.

Spleen size will be measured before transplantation by tomodensitometry scan.

After confirming that patient and his donor are still eligible for transplantation procedure and if the total spleen size remains > 20 cm, a splenectomy must be organized in the following 30 days.

RUXOLITINIB can be continued.

E. Transplantation

1. Donor identification

At inclusion, high resolution HLA typing for HLA-A, B, C, DRB1, DQB1 is performed in patient and donors research is started.

Patient's potential siblings are contacted to perform in emergency an HLA typing. The results should be available in 4 weeks after HLA typing.

If the patient has no sibling, a research on international file of donor is done as soon as the HLA typing is ready.

An unrelated donor is accepted if he has 9 or 10 HLA identities in high resolution typing.

As soon as a donor is identified, a date of transplantation should be set at 4 months after registration.

Before confirming the transplantation patient and donor eligibilities should be confirmed by the transplantation centre by sending a facsimile to GOELAMS office trials (Annexe 18):

GOELAM Secretary

SECRETARIAT CENTRAL GOELAMS

CHU BRETONNEAU

Service d'hématologie et Thérapie Cellulaire

2 boulevard Tonnellé

37044 TOURS CEDEX 9

Tél. : (33) 247391896 Fax : (33) 247373512

2. RUXOLITINIB management in patients planned to transplantation procedure

As described in "dosage and treatment", RUXOLITINIB must be definitively discontinued one day before starting conditioning regimen after tapering.

3. Conditioning regimen before transplantation

For patients transplanted from an HLA identical 10/10 donor, conditioning regimen consisted in:

Fludarabine 30 mg / m2 / day 3 days on day –2, -3, -4 before HSCT
Melphalan 140 mg/m2 1 days on day – 1 before HSCT

	D-5	D-4	D-3	D-2	D-1	
FLUDARABINE		30mg/m²	30mg/m²	30mg/m²		Transplant
MELPHALAN					140 mg/m²	

For patients transplanted from an HLA identical 9/10 donor, conditioning regimen consisted in:

	D-5	D-4	D-3	D-2	D-1	
FLUDARABINE		30mg/m²	30mg/m²	30mg/m²		
MELPHALAN					140 mg/m²	Transplant
THYMOGLOBULINE	2.5 mg/kg	2.5 mg/kg	2.5 mg/kg	2.5 mg/kg		

This conditioning regimen is applicable in all patients from 18 to 69 years.
In cases of renal failure, fludarabine dose should be decreased according to usual recommendation.

4. GVHD prophylaxis

Cyclosporine will be started IV on day – 1 before HSCT at the dose of 3 mg/kg/day and eventually adjusted to concomitants medications interacting according to policy of each centers.
A dosage will be regularly performed in order to target a 200 to 400 ng/mL in blood.

As soon as the patient can take medication per os, cyclosporine is given per os (double of the dosage IV).
Cyclosporine will be continued until 4 months and progressively tapered every 2 weeks (from 20%) in the absence of GVHD.
Mycophenolate mofetyl will be started on day + 1 post HSCT at a dose of 10 mg / kg third a day or 15 mg/kg BID, per os if possible, otherwise IV.
Mycophenolate mofetyl will be continued until 45 days and progressively tapered every 2 weeks (by 500 mg) in the absence of GVHD.

Thymoglobuline® must be added in patients who received an unrelated HLA mismatch transplant (9/10) at the dose of 2.5 mg/kg/day during 4 days on D-5, D-4, D-3, D-2 before HSCT.

Thymoglobuline® is authorized in patients receiving a graft from an unrelated HLA match donor but **not for patients receiving cells from an HLA-identical matched sibling**

In cases of GVHD, curative treatment consisted in high dose corticosteroids and immunosuppressive management is left to physician and each team discretion.

5. Stem cell source

PB are the preferential source of stem cells. At collection, the dose of CD34+ cells should be $\geq 4 \times 10^6$/kg of body recipient.
BM is accepted. At collection, the dose of total nucleated cells should be $\geq 2 \times 10^8$/kg body recipient.

6. Other medication during transplantation

Anti-infectious prophylaxis and curative treatment and all symptomatic treatment are done according to each centres policy following JACIE and/or EBMT recommendations. All patients should receive Herpes simplex prophylaxis until at least 3 months and a pneumocystis carinii prophylaxis until immunosuppressive arrest according to centres modalities.

All patients who were splenectomized before HSCT should received a prophylaxis against pneumococci without any interruption.
Granulocyte colony stimulating growth factor should not be systematically prescribed but if the patient had still ANC < 0.5 G/L 14 days after HSCT, G-CSF are authorized.

VII. Patients assessment

A. Baseline assessment (D1)

At time of registration, patient and disease must be evaluated by the following tests or clinical examination (registration visit):

Clinical visit:

- General examination
- Vital signs (pulse, blood pressure, respiratory rate)
- Weight and height

Performance status evaluated by ECOG

General symptoms related to MF evaluated by MF SAF (Annexe 4)

Spleen size measured by palpation (imagery authorized if the spleen is not easily palpable)

Quality of live questionnaire (Annexe 11)

Hematological assessment:

- Bone marrow biopsy <u>if not performed the previous 6 months</u> (required for diagnosis) or if a transformation into acute leukemia is suspected
- -Cytogenetic analysis of bone marrow or blood if not performed the previous 6 months
- -JAK2V617F and MPL status centralized in hôpital Saint-Louis, Paris.
- -Blood cells count: PLT, ANC, lymphocytes, monocytes, hemoglobin, blasts

Comorbidity assessment according to pregraft HSCT score

Checking for **previous diseases and their date of diagnosis**:

- solid tumor
- inflammatory bowel disease
- inflammatory rheumatological disease
- ongoing infection required treatment
- diabetes requiring treatment (not diabete requiring only diet)
- previous transient ischemic attack or cerebrovascular accident
- peptic ulcer on treatment, psychiatric disturbance including anxiety or depression requiring medical consult or treatment
- cardiac disease
- venous or arterial thrombosis or pulmonary embolism
- liver biological test: AST, ALT, bilirubin, GGT, PAL, LDH
- renal function (creatininemia)
- **cardiac ultrasound** for EF measure and research of valve disease
- ECG
- Oxymetry
- Clinical assessment of dyspnea (**annexe 14**)

Blood sample for genetic and non genetic research (MPL mutation, cytokine, immunology)

<u>HLA typing in high resolution: HLA –A, -B, -C, -DRB1, -DQB1</u>

B. Follow-up between D1 and D 120 or until the date of transplantation

Clinical visit will be done on D1, D15, D30, D60, D90, D120:

- General examination
- Vital signs (pulse, blood pressure, respiratory rate)
- Weight

General symptoms related to MF evaluated by MF SAF (**Annexe 4**) on D30, D60, D90

Performance status evaluated by ECOG (**Annexe 3**) on D30, D60, 90

QOL questionnaire on day 90 (**Annexe 11**), must be before transplantation if the patient is planned to transplantation

Spleen size should be measured:

- on day 30 by palpation (imagery authorized if the spleen is not easily palpable)
- on day 60 by **tomography scan** (which can be the tomography scan for pregraft tests) and by palpation for other patients. In cases of patients planned to transplantation still presenting a splenomegaly > 20 cm on day 60, a first contact with surgeon and anaesthesiologist should be taken in order to schedule the splenectomy on day 90
- on day 90 by palpation. For patients planned to transplantation, if the spleen has decreased below 20 cm, the splenectomy can be cancelled, otherwise, the patient should be splenectomized (in the absence of surgery contraindication).

Biological surveillance:

Blood cell count weekly until day 30 and twice a month until day 120 except for patients with PLT < 100 G/L, ANC < 1G/L, HB < 8 gr/dl for whom blood numeration must be weekly.

Standard biology (creatininemia, ALT, AST, bilirubin, GGT, LDH, PAL) will be performed monthly.

Donor identification:

A date of transplantation should be planned **on day 120** if a donor HLA compatible and eligible has been recruited.

Pregraft tests:

When the transplantation has been planned, pregraft tests can be done from D60 to one week before conditioning regimen, they include usual tests in this context: PFT, cardiac ultrasound, sinus, cerebral, thoracic and abdominal tomodensitometry, biological tests including mandatory serologies and ABO group

Comorbidity assessment according to pregraft HSCT score

Between D60 and D100 and before transplantation comorbidity must be assessed.

checking for **previous diseases and their date of diagnosis**:

- solid tumor
- inflammatory bowel disease
- inflammatory rheumatological disease
- ongoing infection required treatment
- diabetes requiring treatment (not diabete requiring only diet)
- previous transient ischemic attack or cerebrovascular accident
- peptic ulcer on treatment, psychiatric disturbance including anxiety or depression requiring medical consult or treatment
- cardiac disease
- venous or arterial thrombosis or pulmonary embolism
- liver biological test: AST, ALT, bilirubin, GGT, PAL, LDH
- renal function (creatininemia)
- **cardiac ultrasound** for FEVG measure and research of valve disease
- ECG
- Oxymetry
- Clinical assessment of dyspnea (**annexe 14)**

Blood sample for genetic and non genetic research (cytokine, immunology). Blood samples will be collected **at day 90** (must be before transplantation if the patient is planned to transplantation) (**Annexe 12 and 13**)

-**JAK2V617F and MPL status** on day 90 if positive on day 1

The date of transplantation in patients eligible for transplantation should firmly confirmed and eventually adapted if the patient should be splenectomized (spleen > 20 cm)

C. D150 (M5) and D180 (M6) post inclusion or D30 and D60 post transplantation assessment

For the time points after the transplantation, it is preferable to consider D0 as the day of transplantation and all the days after the transplantation D30, D60, D90, D120, D365 (12 months post transplantation), D488 (16 months post transplantation), D610 (20 months post transplantation)

Clinical visit on D150 (M5) post inclusion for the non-transplanted patients and D30 post transplantation for the transplanted patients:

- General examination
- Vital signs (pulse, blood pressure, respiratory rate)
- Weight

Spleen size by palpation on D150 (M5) post inclusion for the non-transplanted patients and D30 post transplantation for the transplanted patients

Biological tests:

-blood cells count on D150 (M5) and D180 (M6) post inclusion for the non-transplanted patients and D30 and D60 post transplantation for the transplanted patients

-standard biology (creatininemia, ALT, AST, bilirubin, GGT, LDH, PAL) on D150 (M5) post inclusion for the non-transplanted patients and D30 post transplantation for the transplanted patients

-only for transplanted patients, blood chimerism is recommended on D30 and D60 post transplantation

D. D120 (M7) post inclusion or D90 (M3) post transplantation assessment to this end of the study (24 months)

These evaluations should correspond to D210 (M7), D305 (M10), D490 (M16), D610 (M20) and D730 (M24) post inclusion in non-transplanted patients or to D90 (M3), D180 (M6), D365 (M12), D610 (M20) post transplantation.

Clinical visit on D210, D305, D490, D610, D730 post inclusion for non transplanted patients and on D90, D180, D365, D610 post transplantation for transplanted patients**.**

- General examination
- Vital signs (pulse, blood pressure, respiratory rate)
- Weight

Performance status evaluated by ECOG (annexe 3): on D210, D305, D490, D610, D730 post inclusion for non transplanted patients and on D90, D180, D365, D610 post transplantation for transplanted patients

General symptoms evaluated by MF SAF (annexe 4) on D210, D305, D490, D610, D730 post inclusion for non transplanted patients and on D90, D180, D365, D610 post transplantation for transplanted patients

Questionnaire for QOL evaluation (annexe 11) on D210 and D490 post inclusion or D90 and D365 (M12) post transplantation and at the end of the study (24^{th} months).

Spleen size for non-splenectomized patients measured by palpation (imagery authorized if the spleen is not easily palpable): D210, D305, D490, D610 and D730 post inclusion or D90, D180, D365, D488, D610 post transplantation.

Haematological assessment:

Blood cells count: PLT, ANC, lymphocytes, monocytes, hemoglobin, blasts on D210, D305, D490, D610 and D730 post inclusion or D90, D180, D365, D488, D610 post transplantation.

JAK2V617F quantification and MPL status in patients with one of these mutations at the inclusion (centralized in Hôpital Saint-Louis) on D210 and D490 post inclusion or D90 and D365 post transplantation only in patients with the mutation at time of registration.

Blood chimerism in transplanted patients on D90, D180, D365 and D610 post transplantation

Standard biology (AST, ALT, bilirubin, GGT, PAL, LDH, creatininemia) on D210, D305, D490, D610, D730 post inclusion or D90, D180, D365 and D610 post transplantation

Blood sample for cytokine, immunology study and biological collection (centralized in hôpital Saint-Louis, Paris) on D210, D490 post inclusion or on D90, D365 post transplantation

Table 12. Resuming clinical and biological tests for the protocol

Time from registration	**D1**	**D30 M1**	**D60 M2**	**D90 M3**	**D120 M4**	**D150 M5**	**D180 M6**	**D210 M7**	**D305 M10**	**D490 M16**	**D610 M20**	**D730 M24**
Time from HSCT	**D-120 M-4**	**D-90 M-3**	**D-60 M-2**	**D-30 M-1**	**D0**	**D30M1**	**D60M2**	**D90M3**	**D180M 6**	**D365 M12**	**D488 M16**	**D610 M20**
Inform consent	**X**											
Clinical visit	**X**	**X2/M**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Spleen size by palpation	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**
ECOG & MF SAF	**X**	**X**	**X**	**X**				**X**	**X**	**X**	**X**	**X**
Blood cell counts	**X**	**X1/W**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Standard biology[1]	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**
Bone marrow biopsy	**X[2]**											
Cytogenetic	**X[3]**											
JAK2V617F and MPL [4]	**X**			**X**				**X**		**X**		
Respiratory assessment[5]	**X**			**X**								
Cardiac assessment[6]	**X**			**X**								
HLA typing	**X**											
Spleen scan			**X**									
Pregraft tests[7]			**X**	**X**								
Co-morbidity Sorror	**X**			**X**								
Cytokine and immunology[8]	**X**			**X**				**X**		**X**		
Quality of life	**X**			**X**				**X**		**X**		**X**
Postgraft blood chimerism						**X**	**X**	**X**	**X**	**X**		**X**
Confirming date of HSCT[9]		**X**	**X**	**X**								

1-creatininemia, ALT, AST, bilirubin, GGT, LDH, PAL
2-bone marrow biopsy is done only if not performed the 6 months preceding inclusion. During the follow-up, bone marrow biopsy is kept to physician discretion
3-blood and/or bone marrow cytogenetic
4-JAK2 status (mutation V617) and quantification for all patients only if positive on day 1, centralization in Hôpital Saint-Louis
5-respiratory assessment includes respiratory rate, dyspnea according to NYHA and oxymetry
6- cardiac assessment includes ECG and echography
7-pregraft tests are usual and legal tests including serology and pulmonary function tests and can be performed 1 to 60 days before HSCT
8-cytokine measure and a biological collection centralized in Hôpital Saint-Louis (annexe 12 - 13)
9- At each visit, date of transplantation should be planned or confirmed if patients and a donor are eligible for transplantation

NB: Time from HSCT can vary according to donor availability, pregraft tests, splenectomy and other unpredictable factors but maximal efforts will be done to perform the transplantation 4 to 5 months after inclusion.

VIII. Safety monitoring and reporting

A. Adverse events

1. Definition of adverse event

For the purposes of this protocol an Adverse Event (AE) is defined as the de novo appearance or worsening of any pre-existing undesirable sign(s), symptom(s), or medical condition(s) that occur after patient has signed the informed consent. Abnormal laboratory values or test results occurring after the signature of the informed consent constitute AE. AEs should be recorded in the Adverse Events module of the eCRF. Conditions that had already been present at the time of informed consent signing should be recorded in the Medical History module of the eCRF. AEs should be described in terms of a diagnosis rather than individual manifestations thereof (signs, symptoms, test result, etc) whenever possible; otherwise the individual manifestations should be reported as individual AEs.

2. Reporting an adverse event

Adverse Events (AEs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. If a CTCAE grading does not exist for the given AE, the severity grades of mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening (grade4),will be used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected by means of a Death Form. The occurrence of AEs should be established by indirect interviewing of the patient during the screening process after signing of the informed consent and at each visit during the study. AEs may also be spontaneously volunteered by the patient during the screening process or between visits, revealed by physical examination, laboratory tests, or other investigations. Each AE should preferably be documented with the following elements:

- The severity grade (CTCAE grades 1-4)
- Causality to the AE (reasonable possibility versus no reasonable possibility that the AE is related to the study drug). Given its open-label character, the sole causal relationship will be assessed for the study drug, RUXOLITINIB. Relevant only to study centers in the EU, should **the AE fulfill at least one seriousness criterion (see section B.1 below), the causality assessment process of RUXOLITINIB must** comply with requirements of the EU Clinical Studies Directive;
- Start as well as end dates (unless unresolved at the follow-up visit);
- Action taken with respect to the study drug (i.e., none, dose adjusted, temporarily interrupted, permanently discontinued, unknown);
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

SAEs are monitored continuously and have special reporting requirements (see "Serious Adverse Event" section below).

Complications related to transplantation itself occurring within 30 days after drug withdrawal should not be reported as AEs unless they fulfill seriousness criteria (see "Serious Adverse Event" section below); an exception constitute **severe adverse events expected in the wake of the bone marrow conditioning regimen. Complications related to transplantation itself occurring more than 30 days after study drug discontinuation should not be considered as AEs.**

B. Serious adverse events

1. Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose fulfils any of the following criteria:

- Is fatal;
- Is life-threatening;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly/birth defect;
- **Requires inpatient hospitalization or prolongation of existing hospitalization, <u>unless indicated for</u>:**
  - **Routine treatment or monitoring of MF;**
  - **The transplantation procedure;**
- Elective or pre-planned treatment for a pre-existing condition other than and unrelated to the indication under study and has not worsened since signing the informed consent;
- Treatment on an emergent event on an outpatient basis that does not result in inpatient admission and not fulfilling any of the other seriousness criteria listed above;
- Social reasons and respite care in the absence of any deterioration in the patient's general condition (hospitalization for non-medical reasons)
- Is medically significant, defined as not fulfilling any of the previously-enumerated criteria yet it is judged by the investigator as potentially jeopardizing the patient and / or possibly requiring medical or surgical intervention to prevent any of the above.
- Pregnancy occurring after signing of the informed consent should be reported as SAE. Similarly, overdose of the study drug, even in the absence of an AE, should be reported as SAE
- Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAE in which a causal role of the study drug is considered a reasonable possibility and not stipulated in IB in terms of nature, intensity, and outcome.

2. Reporting a SAE

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and **until at least 30 days after the patient has stopped RUXOLITINIB, must be reported to the Sponsor within 24 hours of learning of its occurrence**. Any SAEs occurring after this 30-day period should only be reported to the Sponsor if the Investigator suspects a causal relationship with the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original report within 24 hours of the Investigator becoming aware of them. A SAE occurring at a different time point and considered completely unrelated to a previously reported SAE should be reported separately as a new SAE.

The reporting of SAEs that occur between the signing of the informed consent and 30 days following the last administered dose of RUXOLITINIB must be reported by investigators within 24 hour of becoming aware of them (immediate notification) using the SAE report form (Annexe 16) by faxing it to:

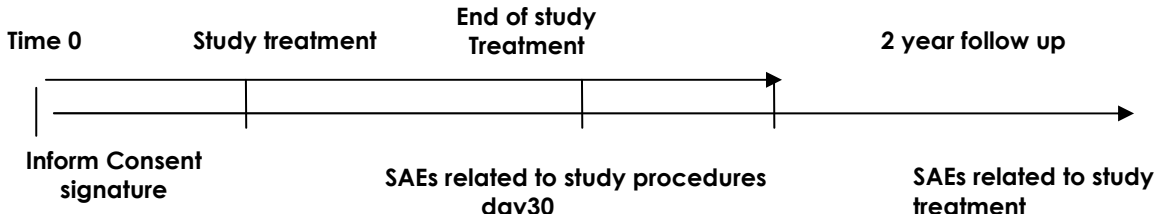
Coordination Center
GOELAMS- study central office[1]
Service d'Hématologie et de Thérapie Cellulaire
Pôle HENRY KAPLAN Hopital Bretonneau
37044 TOURS Cedex 9
Tél. (33)2 47 39 18 96 – Fax : (33)2 47 37 35 12

All SAEs are to be followed until resolution. Study drug-related SAEs will continue to be reported to the Sponsor for as long as the patient is being followed for it.

Investigators are requested to supply detailed information regarding the SAE at the time of initial contact and every subsequent follow-up.

SAE reporting period

SAEs must be reported throughout the period between the date of signing the informed consent and 30 days after the last administration of study drug. After this 30-day period SAEs considered as possibly related to the study drug by the investigator should be reported.



3. Annual Safety Reports

The sponsor must draft Annual Safety Reports (ASR) at every anniversaries of the birthday date of the authorization imparted by the first Competent Authority, inclusive of the following items:

- a listing of all SAEs that were reported during the given annual period;
- a safety analysis and conclusions.

4. Independent Data Safety Monitoring Board

A Data Safety Monitoring Board will examine throughout the study all AEs and SAEs, whether expected or unexpected, whether related or not to RUXOLITINIB. This committee will meet at the time of the annual safety report by teleconference and in case of an abnormal rate of SAE incidence. The DSMB write also the conclusion of the safety analyse in the annual safety reports subsequently addressed to the concerned Ethic Committees and Competent Authorities.

The members of the DSMB are identified on a separate document.

IX. Data review and management

A. Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

B. Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, Sponsors' personnel (or designated CRO) will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

C. Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using the webtrial solution….

The Investigators and co-investigators are responsible for the accuracy of these data. Each investigator will receive a login and password.

D. Data analysis

Data analysis will be performed from data extracted from the eCRF. The latter has been built in accordance with the trial schedule and according to ongoing legislation.

E. Data storage

Data storage will be performed according to national procedure. A PDF version of each eCRF will be accessible for electronic or hardcopy storage.

X. Statistical considerations

A. Calculation of number of patients according to primary objective

The primary objective is to demonstrate that DFS 12 months after HSCT is higher than 50% in patients who received a treatment by RUXOLITINIB before HSCT. The trial would be designed to test this hypothesis P $\leq$ 50% versus P$\geq$70% with one sided type I error rate 5% and power 90% with A'Hern's method for a binomial test (A'Hern 2001), **53 patients should be transplanted**. The analysis will be based on a binomial test comparing the observed 12 months DFS to 50%. **Enrollment will be stopped as soon as 53 patients received a HSCT**.

B. Estimation of total number of patient recruited

The probability to found a donor in French patients is about 70% (HLA matched sibling or unrelated donor with 9 or 10 HLA identities). That means that for 53 transplanted patients, 23 other patients will not have a donor and will constitute the "arm without donor". Furthermore, some patients with a donor, can be excluded from transplantation procedure (death, acquisition of a contraindication for transplantation) and 5 to 10% additional patients with donor may be required to achieve the 53 patients transplanted. That means that 76 to 80 patients should be included in the study.

To respond to one of the secondary objectives of the study, namely, the complete hematological remission, our hypothesis is that 50% of patients with donor compared to 10% in patients without a donor will obtain a complete remission. If the study included 53 patients with donor and 23 patients without donor, the number of patients is sufficient to respond to this objective with a 80% power. The statistical analysis will be done in intent to transplant considering patients with or without donor.

C. Stopping rules

Stopping rules based on the incidence of toxic death occurring during the first 60 days will be implemented according to the method proposed by Kramar and Bascoul-Mollevi (Kramar and Bascoul-Mollevi 2009).

Toxic death is defined as a death non related to relapse or event foreign to somatic medical condition (accident, suicide). All deaths from infections, acute GVHD, hematological disorder other than relapse, organ failures are considered as "toxic death".

The maximum acceptable rate of toxic death during the **first 60 days postHSCT will be fixed at 15%**, and the type I error α at 5%. Briefly, the method computes a lower boundary for the number of patients included when observing increasing numbers of adverse events, based on exact one-sided 100(1- α)% confidence intervals with a concave α -spending function to control the overall type I error rate of this analysis despite repeated confidence intervals calculations.

Each type an adverse event is observed, the number of patients included with minimal follow-up of one day is compared to the lower boundary, and a recommendation to stop the trial will be emitted if this number is under the boundary.

D. Statistical analysis of the data

The main analysis will be based on a binomial test comparing the observed 12 months DFS to 50%. The DFS at 12 months will be presented with its 90% confidence interval, which is consistent with a one-sided test with a 5% type I error rate.

Overall survival and disease free survival curves will be estimated using Kaplan-Meier product-limit estimator. Cumulative incidence curves of haematological response, transfusion independency, acute graft-versus-host disease, infection and non-relapse death will be estimated using usual estimator. Results will be presented together with pointwise 95% two-sided confidence intervals.

In transplanted patients, prognostic factors of disease free survival will be analysed using Cox proportional hazards models.

Endpoints in patients with and without donor will be compared according to an intent-to-transplant principle: patients with a donor but not transplanted because of change or medical condition before transplant or who died before transplant will be analysed in the “patients with donor” group.

Characteristics of patients with and without donor will be compared using Wilcoxon rank-sum tests and Fisher's exact tests.

Cumulative incidences of haematological response and transfusion independency will be compared between patients with and without donor using Gray’s tests (Gray 1988). The hazards of death and relapse or death and the cause-specific hazards of infection will be compared between patients with and without donor using proportional hazards (Cox) models.

All these test involving comparison of patients with and without donor will be two-sided, with a 5% type I error rate.

For transplanted patients, clinical outcomes from date of transplantation will be ANC and PLT engraftment, acute and chronic GVHD (see previous definitions), DFS, NRM and OS.

All time-to-event outcomes will be counted from the date of transplantation to the date of event or date of last follow-up, ie: 24 months postinclusion, except engraftment and acute GVHD that will bey censored at 200 days postHSCT (no possible events after this date). NRM is considered as any death occurring before disease relapse/progression. DFS is defined as survival time to relapse or death. Death is considered as a competing risk in analyses of engraftment and acute GVHD. NRM and relapse are considered to be mutually competing risks. OS and DFS functions will be estimated using Kaplan-Meier product-limit estimator. For competing risks analyses, cumulative incidence functions (engraftment, GVHD incidence, NRM) will be estimated using usual methodology (Kalbeisch and Prentice 1980).

Factors associated with outcomes will be analyzed using Gray's tests (acute GVHD), proportional hazards models for the cause-specific hazard (Prentice*, et al* 1978) (relapse and NRM) and Cox proportional hazards models (DFS and OS). The proportional hazards assumption will be checked by examination of Schoenfeld residuals and Grambsch and Therneau's lack-of-fit test (Grambsch and Therneau 1994).

All tests will be two-sided and P-values < 0.05 will be considered as indicating significant association. Analyses will be performed using the R statistical software version 2.10.1 R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria 2009. URL http://www.R-project.org. ISBN 3-900051-07-].

Analyses were performed using the R statistical software version 2.10.1.R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria 2009. URL http://www.R-project.org. ISBN 3-900051-07-0.

XI. Ethical considerations and administrative procedures

This protocol was designed and will be conducted, recorded, and reported in compliance with the current ICH/GCP guidelines and local ethical and legal requirements.

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and its amendments laid down in Tokyo, Hong-Kong, Venise, Somerest and Edimbourg (Addundum Washington 2002, Tokyo 2004), and with the law of the French Public Health (Provisions of French Act n° 88-1138 of the 20.12.1988, and Act 2004-806 of the 9 août 2004, Code de la Santé Publique).

This protocol is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

This protocol and patient informed consent form must be reviewed and approved by an IRB/ Institutional Ethics Committee (Comité de Protection des Personnes) complying with applicable national and international regulations before enrollment of patients.

A. Informed consent

Written informed consent is obtained by each patient before inclusion into the study. Using patient information sheets, as well as personal oral explanation by a local investigator at the patient's transplant center, the patient will be informed of the aims and the investigational nature of the study, the exact procedures that will be done during treatment and evaluation, the possible risks and side effects, and of alternative treatment options. They will be informed as to the strict confidentiality of their patient data, but that authorized individuals other than their treating physician may review their medical records for trial purposes. Further, the patient will be informed that their anonymized data will be scientifically analyzed and published.

It will be emphasized that the participation is voluntary and that consent can be withdrawn by the patient at any time without explanation of the reason. The patient is allowed to refuse further participation in the protocol, whenever he/she wants. The patient's further treatment will not be influenced by this decision.

B. Insurance

The sponsor states having taken out an insurance policy covering, according to clauses in the policy and within the limit of sums determined the pecuniary consequences of their civil liability as resulting from application of Article L.1121-10 of the French Public Health Code. The policy covers in particular investigators as well as all of their coworkers and assistants carrying out clinical trials in accordance with current law. Taking out of such a policy by the sponsor does not deprive the sponsor of rights of recourse against the above-mentioned individuals should they commit any errors.

C. Amendments and protocol

Any change to the protocol must form the basis of an amendment or an information memorandum to Ethics Committee and a competent authority. It will take effect only after approval of the CPP and authorization of AFSSAPS. Information leaflets and patient consent forms must be modified if required.

D. Patient confidentiality

By signing this protocol, the main investigator and all co-investigators undertake to keep confidential the identities of patients participating in the study. A case report form number will be assigned to the patient. The first three letters of the last name, first two letters of the first name and the date of birth will be the only information indicated on the case report form and which will make it possible later to associate the case report form with the patient concerned.

This research project has formed the basis of a request for authorization sent to the CNIL (Commission Nationale Informatique et Libertés/National Information Technology and Civil Rights Commission) by application of the “Information technology and civil rights” acts (Act no. 78-17 of the 6/01/1978 and act no. 2004-801 of the 6/08/2004). Medical data may be sent only to the department responsible for data entry, under responsibility of the sponsor, and possibly to appropriate health care authorities under conditions guaranteeing data protection.

The sponsor and government authorities may request direct access to medical records to check procedures and/or data from the clinical trial, without violating confidentiality and within limits permitted by laws and regulation.

E. Publication policy

All data generated from this study are the property of the FIM/SFGMTC/GOELAMS group and shall be held in strict confidence. Analysis and/or publication of these data by an Investigator are not permitted without prior consent from the FIM/SFGMTC/GOELAMS group. Permission to the Investigator will be contingent on the review by the FIM/SFGMTC/GOELAMS group of the statistical analysis and manuscript. All manuscripts and abstracts will be submitted to the FIM/SFGMTC/GOELAMS group 30 days prior to submission.

LISTE DES ANNEXES

Annexe 1. WHO diagnosis for myelofibrosis

✓ WHO classification for primary myelofibrosis (Tefferi, *et al* 2007, Vardiman, *et al* 2009)

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

Major criteria

1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV, CML, MDS or other myeloid neoplasm
3. Demonstration of *JAK2*617V>F mutation or other clonal marker (eg, *MPL*515W>L/K),

or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases¶

Minor criteria

1. Leukoerythroblastosis
2. Increase in serum lactate dehydrogenase level
3. Anemia
4. Palpable splenomegaly

✓ WHO classification for secondary myelofibrosis (Barosi, *et al* 2008)

Criteria for post-essential thrombocythemia myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1]
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):

1. Anemia[b] and a $\geqslant 2\,mg\,ml^{-1}$ decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geqslant 5$ cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above reference level)
5. Development of $\geqslant 1$ of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5°C$)

Criteria for post-polycythemia vera myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1]
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):

1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geqslant 5$ cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of $\geqslant 1$ of three constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5°C$)

Annexe 2. Medications interacting with CYP3A4

1. Medications that can induce CYP3A4

Strong inducers	Moderate inducers	Weak inducers	Unclassified inducers
Avasimibe	bosentan	Amprenavir	topiramate
Carbamazepine	efavirenz	Aprepitant	
Phenobarital	etravirine	armodafinil (R-modafinil)	
Phenytoin	modafinil	Dexamethasone	
Rifabutin	nafcillin	Echinacea	
Rifampin	ritonavir	Garlic	
St. John's wort	talviraline	Gingko	
	tipranavir	Glycyrrhizin	
		Methylprednisolone	
		Nevirapine	
		Oxcarbazepine	
		Pioglitazone	
		Prednisone	
		Pleconaril	
		Rufinamide	
		Troglitazone	

Note:

Inducer classification:

- Strong inducers may result in a substrate AUC decreased by ≥ 80%.
- Moderate inducers may result in a substrate AUC decreased by 50-80%.
- Weak inducers may result in a substrate AUC decreased by 20-50%.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

2. Medications that can inhibit CYP3A4

Strong inhibitors	Moderate inhibitors	Weak inhibitors
Clarithromycin	Amprenavir	alprazolam
Conivaptan	Aprepitant	AMD070
Indinavir	Atazanavir	amlodipine
Itraconazole	Cimetidine	azithromycin
Ketoconazole	Ciprofloxacin	bicalutamide
Lopinavir	Darunavir	cranberry juice
Mibefradil	Diltiazem	chlorzoxazone
Nefazodone	Elvitegravir	cilostazol
Nelfinavir	Erythromycin	cyclosporine
Posaconazole	Fluconazole	fluvoxamine
Ritonavir	grapefruit juice	ginkgo
Saquinavir	Imatinib	goldenseal
Telithromycin	schisandra sphenanthera	isoniazid
Troleandomycin	Tipranavir	lacidipine
Voriconazole	Tofisopam	M100240
Posaconazole	Verapamil	nilotinib
		oral contraceptives *(e.g. drospirenone, norgestimate, and ethinyl estradiol)*
		peppermint oil
		propiverine
		ranitidine
		ranolazine
		roxithromycin
		Seville orange juice
		sitaxentan
		tabimorelin

Note:
Inhibitor classification:

- Strong inhibitors may result in a substrate AUC > 5-fold increase.
- Moderate inhibitors may result in a substrate AUC ≥ 2-fold increase and < 5-fold increase.
- Weak inhibitors may result in a substrate AUC ≥ 1.25-fold increase and < 2-fold increase.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details

Annexe 3. Eastern Cooperative Oncology Group Performance Status Criteria

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Reference for ECOG (Oken, *et al* 1982)

Annexe 4. Myelofibrosis Screening Symptom Form

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 symptomes où:

- 0 est l'absence total de symptomes,

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

Symptomes 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)

Annexe 5. Pregraft comorbidities definitions and score (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.

Annexe 6. Acute GVHD classification adapted from Glucksberg et al (Glucksberg, et al 1974)

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

Annexe 7. Chronic GVHD classification according to Shulman et al (Shulman, et al 1980)

Limited chronic GVHD:

Either or both criteria must be present:

- Localised skin involvement
- Hepatic dysfunction

Extensive chronic GVHD :

Either:

- Generalised skin involvement

or

- Localised skin involvement and / or hepatic dysfunction
- plus liver histology showing chronic aggressive hepatitis,

bridging necrosis or cirrhosis

or

Involvement of eye: Schirmer's test with < 5 mm wetting,

or

Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy specimen,

or

Involvement of any other target organ (e. g., oesophageal abnormalities, polymyositis)

Annexe 8. Definitions of invasive fungal infections

Table 1. Definitions of invasive fungal infections in patients with cancer and recipients of hematopoietic stem cell transplants.

Category, type of infection	Description
Proven invasive fungal infections	
Deep tissue infections	
Molds[a]	Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes
Yeasts[a]	Histopathologic or cytopathologic examination showing yeast cells (*Candida* species may also show pseudohyphae or true hyphae) from specimens of needle aspiration or biopsy excluding mucous membranes; or positive culture result on sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes; or microscopy (India ink, mucicarmine stain) or antigen positivity[b] for *Cryptococcus* species in CSF
Fungemia	
Molds[a]	Blood culture that yields fungi, excluding *Aspergillus* species and *Penicillium* species other than *Penicillium marneffei*, accompanied by temporally related clinical signs and symptoms compatible with relevant organism
Yeasts[a]	Blood culture that yields *Candida* species and other yeasts in patients with temporally related clinical signs and symptoms compatible with relevant organism
Endemic fungal infections[c]	
Systemic or confined to lungs	Must be proven by culture from site affected, in host with symptoms attributed to fungal infection; if culture results are negative or unattainable, histopathologic or direct microscopic demonstration of appropriate morphological forms is considered adequate for dimorphic fungi (*Blastomyces, Coccidioides* and *Paracoccidioides* species) having truly distinctive appearance; *Histoplasma capsulatum* variant *capsulatum* may resemble *Candida glabrata*
Disseminated	May be established by positive blood culture result or positive result for urine or serum antigen by means of RIA [17]
Probable invasive fungal infections	At least 1 host factor criterion (see table 2); and 1 microbiological criterion; and 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection
Possible[d] invasive fungal infections	At least 1 host factor criterion; and 1 microbiological or 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection

[a] Append identification at genus or species level from culture, if available.
[b] False-positive cryptococcal antigen reactions due to infection with *Trichosporon beigelii* [1], infection with *Stomatococcus mucilaginosis* [2], circulating rheumatoid factor [3], and concomitant malignancy [4] may occur and should be eliminated if positive antigen test is only positive result in this category.
[c] Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis.
[d] This category is not recommended for use in clinical trials of antifungal agents but might be considered for studies of empirical treatment, epidemiological studies, and studies of health economics.

Annexe 9. Monitoring of infections

Infections which should be considered:

-pneumonia

-severe sepsis defined in **Annexe 10**

-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

-Adénoviral reactivation

Annexe 10. Definition of severe sepsis: at least 2 criteria A and one criteria B

Critères A	-Cardiac pulse > 90/mn -Respiratory frequency > 20/mn -Mechanical ventilation -Temperature > 38 C or < 36 C
Critères B	-Systolic blood pressure< 90 mmHg -Diuresis < 30ml/h ou < 700 ml/24h -PaO2 < 75 mmHg or PaO2/FiO2< 250 -Encephalopathy (Glasgow score < 14) -Meabolic acidosis -Coagulopathy

Annexe 11. EORTC version 3 Quality of life

http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_c30.pdf

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de «bonne» ou de «mauvaise» réponse. Ces informations sont strictement confidentielles.

Au cours de la semaine passée (7 jours) :

		Pas du tout	Un peu	Assez	Beaucoup
1.	Avez-vous de difficultés à faire certains efforts physiques pénibles comme porter un sac à provision chargé ou une valise?	1	2	3	4
2.	Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
3.	Avez-vous des difficultés à faire un petit tour dehors?	1	2	3	4
4.	Etes-vous obligé(e) de rester au lit ou dans un fauteuil pendant la journée?	1	2	3	4
5.	Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes?	1	2	3	4
6.	Avez-vous été gêné(e) pour faire votre travail ou vos activités de tous les jours?	1	2	3	4
7.	Avez-vous été gêné(e) dans vos activités de loisirs?	1	2	3	4
8.	Avez-vous eu le souffle court?	1	2	3	4
9.	Avez-vous ressenti de la douleur?	1	2	3	4
10.	Avez-vous eu besoin de repos?	1	2	3	4
11.	Avez-vous eu des difficultés pour dormir?	1	2	3	4
12.	Vous êtes-vous senti(e) faible?	1	2	3	4
13.	Avez-vous manqué d'appétit?	1	2	3	4
14.	Avez-vous eu des nausées (mal au coeur)?	1	2	3	4
15.	Avez-vous vomi?	1	2	3	4
16.	Avez-vous été constipé(e)?	1	2	3	4

		Pas du tout	Un peu	Assez	Beaucoup
17.	Avez-vous eu de la diarrhée?	1	2	3	4
18.	Etiez-vous fatigué(e)?	1	2	3	4
19.	Des douleurs ont-elles perturbé vos activités quotidiennes?	1	2	3	4
20.	Avez-vous eu des difficultés à vous concentrer sur certaines choses, par exemple, pour lire le journal ou regarder la télévision?	1	2	3	4
21.	Vous êtes-vous senti(e) tendu(e)?	1	2	3	4
22.	Vous êtes-vous fait du souci?	1	2	3	4
23.	Vous êtes-vous senti(e) irritable?	1	2	3	4
24.	Vous êtes-vous senti(e) déprimé(e)?	1	2	3	4
25.	Avez-vous eu des difficultés pour vous souvenir de certaines choses?	1	2	3	4
26.	Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans votre vie familiale?	1	2	3	4
27.	Votre êtat physique ou votre traitement médical vous ont-ils gêné(e) dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma…)?	1	2	3	4
28.	Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers?	1	2	3	4

Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation:

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée?

Très mauvais						Excellent
1	2	3	4	5	6	7

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée?

Très mauvais						Excellent
1	2	3	4	5	6	7

Les patients rapportent parfois les symptômes ou problèmes suivants. Pourriez-vous indiquer, s'il vous plaît, si, durant la semaine passée, vous avez été affecté(e) par l'un de ces symptômes ou problèmes. Entourez, s'il vous plaît, le chiffre qui correspond le mieux à votre situation.

Au cours de la semaine passée:

		Pas du tout	Un peu	Assez	Beaucoup
31.	Avez-vous eu des douleurs dans la bouche?	1	2	3	4
32.	Avez-vous eu la bouche sèche?	1	2	3	4
33.	Avez-vous eu des difficultés pour avaler?	1	2	3	4
34.	La nourriture et la boisson avaient-elles un goût inhabituel?	1	2	3	4
35.	Avez-vous éprouvé des douleurs ou des crampes abdominales?	1	2	3	4
36.	Avez-vous eu des problèmes de peau (peau sèche, démangeaisons, peau qui pèle)?	1	2	3	4
37.	Vous êtes-vous senti(e) perturbé(e) par l'impact du traitement sur vos cheveux ?	1	2	3	4
38.	Vous êtes-vous fait du souci à cause de votre poids trop faible?	1	2	3	4
39.	Avez-vous eu de la fièvre ou des frissons?	1	2	3	4
40.	Avez-vous uriné fréquemment?	1	2	3	4
41.	Avez-vous éprouvé des maux ou des douleurs dans les os?	1	2	3	4
42.	Vous a-t-il paru difficile de terminer les choses que vous aviez commencées?	1	2	3	4
43.	Vous êtes-vous fait du souci au sujet des résultats des examens et des tests?	1	2	3	4

Veuillez compléter les questions suivantes si vous suivez encore votre traitement à l'hôpital à l'heure actuelle. Si ce n'est pas le cas, passez à la question 48.

Au cours de la semaine passée:

		Pas du tout	Un peu	Assez	Beaucoup
44.	Avez-vous éprouvé des difficultés à supporter le séjour à l'hôpital?	1	2	3	4
45.	L'isolement vous a-t-il troublé(e) à l'hôpital?	1	2	3	4
46.	Avez-vous redouté que vos résultats sanguins (numérations) ne se rétablissent pas?	1	2	3	4
47.	Dans quelle mesure étiez-vous satisfait(e) de la préparation à votre traitement?	1	2	3	4

<u>Au cours des quatres dernières semaines:</u>

		Pas du tout	Un peu	Assez	Beaucoup
48.	Vous êtes-vous senti isolé(e) de vos proches (famille, amis)?	1	2	3	4
49.	Vous êtes-vous inquiété(e) que votre traitement perturbe votre vie de famille?	1	2	3	4
50.	Jusqu'à quel point, d'après vous, la maladie ou votre traitement ont-ils affecté vos proches?	1	2	3	4
51.	Avez-vous ressenti le besoin de cacher vos peurs/soucis à votre famille ou vos amis?	1	2	3	4
52.	Votre expérience vous a-t-elle aidé(e) à faire la différence entre les choses importantes dans la vie et celles qui ne le sont pas?	1	2	3	4
53.	Vous êtes-vous inquiété(e) de votre santé future?	1	2	3	4
54.	Vous êtes-vous senti moins séduisant(e) physiquement à cause de votre maladie ou de votre traitement?	1	2	3	4

Veuillez cocher la case si la question suivante ne vous concerne pas ☐ et passez à la question 56

		Pas du tout	Un peu	Assez	Beaucoup
55.	Vous êtes-vous inquiété(e) du fait d'encore pouvoir avoir des enfants?	1	2	3	4

Veuillez compléter les questions suivantes uniquement si vous avez fini votre traitement à l'hôpital et êtes actuellement à la maison.
Au cours des quatre dernières semaines :

		Pas du tout	Un peu	Assez	Beaucoup
56.	Le fait de devoir prendre des médicaments régulièrement a-t-il eu un impact sur votre vie quotidienne?	1	2	3	4
57.	Vous êtes-vous observé(e) de près pour détecter d'éventuels nouveaux symptômes?	1	2	3	4
58.	Avez-vous éprouvé moins d'intérêt pour le sexe?	1	2	3	4
59.	Avez-vous éprouvé moins de plaisir sexuel?	1	2	3	4

60. Si vous êtes retraité, veuillez cocher la case ☐, sinon quelle profession avez-vous exercé pendant les dernières 12 mois?
Réponse: .....

Avez-vous travaillé à plein temps (100%)? ☐Oui ☐Non
Si non, pouvez-vous indiquer combien de temps (à temps partiel, en %) avez-vous travaillé, s.v.p.?
A temps partiel de .....%

Annexe 12. Method for biological analysis
Diary for biological analysis and collection

	INCLUSION	3 MONTHS	7 MONTHS	16 MONTHS
15 ml Blood samples	**X**	**X**	**X**	**X**
5 ml serum	**X**	**X**	**X**	**X**

JAK2V617F mutation status and allele quantification

The method used in Saint-Louis hospital lab is the JAK2 Mutaquant kit (Ipsogen) to measure allele burden of the JAK2 V617F mutation with a sensitivity of 0.1%. This kit is based on the method described in Lippert et al. (Lippert, *et al* 2006). Briefly, 2 separate mixes are used, each containing a mutant specific or a wild type specific forward primer. The kit also contains JAK2 mutant or wild type plasmid dilutions which are used as standards in order to quantify each form of the JAK2 gene in the sample and then to determine the percentage of JAK2 V617F. As defined in the manufacturer's instructions, the minimum level of JAK2 V617F detection was set at 0.1%.

These analyses will be done by Bruno Cassinat (Biological Trial Coordinator).

MPL W515 mutation detection

The method used in Saint-Louis hospital lab to detect the presence of a mutation in position 515 of MPL is the MPL MutaScreen kit (Ipsogen). It is based on a Real Time PCR using allele specific Taqman probes which are able to discriminate between the wild type allele and the mutated alleles.

These analyses will be done by Bruno Cassinat (Biological Trial Coordinator).

Cytokine and immunological analysis

Serum will be separated by centrifugation, whereas peripheral blood mononuclear cells (PBMCs) will be purified with Lymphoprep (Axis-Shield)density gradient medium.The samples of serum will be analyzed for cytokine production using the Luminex MAP technology. Multiplex assays, allowing the simultaneous detection of several cytokines, exist as commercially available kits (Invitrogen, R&D).
Circulating CD34+ and CD45+ PBMCs will be analyzed by flow cytometry for surface markers. FACSCanto II and LSR Fortessa (BD Bioscience) will allow the detection of respectively up to 8 and 18 different surface markers.
These analyses will be done by Dr. Rachel GOLUB (Maître de conférences, HDR, Université Paris Diderot) and collaborators, Unité de Lymphopoièse, Institut Pasteur, INSERM U668, 25 Rue du Dr Roux, 75724 Paris Cedex 15, Tel: O1 45 68 87 66, Fax: 01 45 68 89 21
rachel.golub@pasteur.fr/rachel.golub@univ-paris-diderot.fr

Annexe 13. Formulaire pour l'analyse biologique JAK ALLO

Nom (3 premières lettres) [__][__][__]

Prénom (2 premières lettres) [__][__] Sexe[__]

Date naissance [__][__] [__][__] [__][__]

Centre : ..... ET n° FAX *(pour confirmation)* : .....

Médecin responsable : Adresse e-mail : .....

INCLUSION	
3 tubes EDTA 5ml	
1 tube sec 5 ml	

3 mois post inclusion ou pré-greffe	
3 tubes EDTA 5ml	
1 tube sec 5 ml	

7 mois post inclusion ou 3 mois post greffe	
3 tubes EDTA 5ml	
1 tube sec 5 ml	

17 mois post inclusion ou 12 mois postgreffe	
3 tubes EDTA 5ml	
1 tube sec 5 ml	

Fiche à faxer au 01 42 38 54 76

Echantillons à envoyer en temperature ambiante du lundi au jeudi

Unité de Biologie Cellulaire

Hôpital Saint-Louis

1 Av. C. Vellefaux, 75010 Paris

Pour toutes informations complémentaires contacter BRUNO CASSINAT

au 01 42 49 92 03 ou Bruno.cassinat@sls.aphp.fr

Annexe 14. New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity. E.g., shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g. walking short distances, ~ >20 - 100m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest, mostly bed bound patients

Annexe 15. Registration form

FICHE D'INCLUSION PROTOCOLE JAK-ALLO

Nom (3 premières lettres) [__][__][__]

Prénom (2 premières lettres) [__][__] Sexe[__]

Date naissance [__][__] [__][__] [__][__]

Centre : ..... ET n° FAX *(pour confirmation)* : .....

Médecin responsable : Adresse e-mail : .....

CRITERES D'INCLUSION

	OUI	NON
Patient avec une myélofibrose primitive ou secondaire à une polyglobulie de Vaquez ou une thrombocytémie essentielle attestée par une biopsie ostéomédullaire de moins de 6 mois	❒	❒
Splénomégalie palpable ou > 15cm d'axe maximal en imagerie	❒	❒
Au moins un critère parmi: (1) hémoglobine < 100 gr/L; (2) leucocytes < 4G/L ou > 25 G/L; (3) blastes sanguins ou de moelle osseuse > 10% mais <20%, (4) anomalie des chromosomes 5, 7 ou 17	❒	❒
Ou symptomes généraux associés à une blastose sanguine > 1%	❒	❒
PS : ECOG 0, 1 ou 2	❒	❒
FEV cardiaque > 40 %	❒	❒
Age entre 18 et 69 ans inclus	❒	❒
Clairance de la créatinine > 30 ml/min	❒	❒
Bilirubin < 2 UI et transaminases < 5 UI	❒	❒
Dyspnée stade 0, I, II (NYHA)	❒	❒
Index de comorbidité 0, 1, 2 ou 3	❒	❒
Patient apte à donner son consentement	❒	❒
Femme n'étant pas enceinte ou allaitante	❒	❒
Etre affilié à l'assurance maladie ou être bénéficiare d'un tel régime	❒	❒
Consentement éclairé signé	❒	❒

CRITERES D'EXCLUSION

	OUI	NON
Transformation de la myélofibrose en LAM	❒	❒
Antériotié de traitement par inhibiteurs de JAK2	❒	❒
Thrombopénie persistante < 50 G/L	❒	❒
Patients ayant une contre indication à l'allogreffe quelqu'elle soit	❒	❒

FAXER au Secrétariat du GOELAMS
Fax: 02.47.37.35.12

Téléphone Secrétariat GOELAMS : 02.47.39 18 96
ou goelams@med.univ-tours.fr

Annexe 16. Serious adverse event form

SERIOUS ADVERSE EVENT (SAE) REPORTING FORM

Sponsor: GOELAMS

Clinical Trial Identification	Eudract N°	Center N°	Investigator N°	Country
JAK ALLO				

Please fax the completed form to the Pharmacovigilance Unit within 48 hours.

Fax N°: 02 47 37 35 12

Type of report: ☐ Initial ☐ Follow-up

Date of SAE reporting to GOELAMS: |_|_|/|_|_|/|_|_| dd/mm/yy

1. PATIENT DATA

Patient initials: |_|_|_| |_|_|

last name *first name*

Birth date: |_|_|/|_|_|/|_|_| dd/mm/yy

Patient N°: |_|_|_|_|

Sex: ☐ M ☐ F

Weight (*kg*): |_|_|_|.|_|

Height (*cm*): |_|_|_|

2. SERIOUSNESS CRITERION

☐ Death If yes, date of death (dd/mm/yy)
|_____| |_____| |_____|

Primary cause of death.....
Was Autopsy performed? ☐No ☐Yes
(if yes, attach copy of report if available)

☐ Life-threatening

☐ Involved or prolonged hospitalization

☐ Congenital anomaly/ birth defect

☐ Persistence or significant disability / incapacity

☐ Medically significant

4. SERIOUS ADVERSE EVENT

Date of onset*: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ Date of hospitalization (if applicable)*: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Description [Include a history of the event chronologically including: signs and characteristics, severity, dates and outcome of hospitalization and any other relevant information not captured elsewhere on the form].

Chronological data relevant for the SAE	Date of inclusion*:	⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
	First administered study drug: Date of first administration of study drug*:	⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
	Randomization arm : (and/or group/subgroup etc.) Chemotherapy phase *(if applicable):*	
	Cycle N°/week at the time of SAE onset *(if applicable):*	⌊_⌋⌊_⌋
	Day of cycle/week *(if applicable):*	⌊_⌋⌊_⌋

*dd/mm/yy

5. ADVERSE EVENTS OF SPECIAL INTEREST (AESI) ☐ Yes – specify bellow ☐ No

defined as any scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate; such events may require further investigation in order to characterize and understand them (CIOMS VI 2005):

6. SERIOUS ADVERSE EVENT OUTCOME (at the time of the report)

		Date*	
Fatal	☐	⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	
Resolved without sequelae	☐	⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	
Resolved with sequelae	☐	⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	Sequelae:
Improved	☐		
Persisting	☐		
Worsened	☐		
Unknown	☐		

* dd/mm/yy

7. STUDY DRUG(S)	(all study treatments specified in the protocol)						
N°	Name	Dose	Frequency	Route	Start date*	Last date before SAE onset*	Ongoing
1							☐
2							☐
3							☐
4							☐
5							☐

* dd/mm/yy

Delay of occurrence after last dose intake: *(number)* __________ *(unit)*

8. ACTION TAKEN WITH STUDY DRUG(S)						
Drug (*N° same as in 7)*	No change	Temporarily interrupted		Permanently stopped	Dose adjusted (*detail*)	Unknown
		Date stopped*	Date restarted*	Date stopped*		
1	☐				☐	☐
2	☐				☐	☐
3	☐				☐	☐
4	☐				☐	☐
5	☐				☐	☐

* dd/mm/yy

9. CONCOMITANT TREATMENT						
Name	Daily dose	Route	Start date*	Last date before SAE onset**	Ongoing	Indication
					☐	
					☐	
					☐	
					☐	
					☐	

* dd/mm/yy

10. CORRECTIVE TREATMENT	(drug, procedures, etc)			
Name	Total daily dose/unit	Start date*	End date*	Ongoing
		⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	☐
		⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	☐
		⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	☐
		⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	☐
		⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	☐

* dd/mm/yy

11. RELEVANT LABORATORY / OTHER DIAGNOSTIC INVESTIGATIONS	Including laboratory values preceding the event			
☐ Yes – specify bellow ☐ No				
Investigation sheet provided separately? ☐ Yes → number of extra pages _____				
Name of test	Results (units)	Normal values / Reference ranges	Sample collection date*	Result pending
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐
			⌊_⌋⌊_⌋⌊_⌋	☐

* dd/mm/yy

12. POSSIBLE CAUSES OF THE EVENT	
Check off all the applicable	Specify
Pre-existing / underlying disease ☐	
Study treatment ☐	
Other treatment (concomitant or previous) ☐	
Protocol-related procedure ☐	
Other (e.g. accident, new or intercurrent illness, etc.) ☐	

13. INVESTIGATOR				
SAE form	Full name (in uppercase letters)	Function	Date*	Signature
filled out by:			⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	
validated by:			⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋	

* dd/mm/yy

Annexe 17. Criteria for response to treatment

Complete response definition

- Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.

-Peripheral blood count remission defined as haemoglobin level at least 110 g/L, PLT count at least 100 G/L, and ANC at least 1 G/L. In addition, all 3 blood counts should be no higher than the upper normal limit.

-Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy.

-Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.

If a transplanted patient has no cytopenias, no constitutional symptoms, no splenomegaly and a 100% donor chimerism, he will be considered in complete remission (and marrow biopsy will not be required).

Partial remission definition

Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Annexe 18. Transplantation confirmation form

CONFIRMATION DE GREFFE - PROTOCOLE JAK-ALLO

Nom (3 premières lettres) [__][__][__] Prénom (2 premières lettres) [__][__] Sexe[__]

Date naissance [__][__] [__][__] [__][__]

Centre : ..... ET n° FAX *(pour confirmation)* : .....

Médecin responsable : Adresse e-mail : .....

	OUI	NON
Un donneur géno-identique a été identifié dans la fratrie.....	❒	❒
Un donneur HLA identique 10/10 a été identifié sur fichiers internationaux.....	❒	❒
Un donneur HLA compatible 9/10 a été identifié sur fichiers internationaux.....	❒	❒
Le donneur compatible ne présente pas de contre indication apparente au don....	❒	❒
Il n'existe pas d'argument pour une transformation de la myélofibrose en leucémie aiguë.....	❒	❒
PS : ECOG 0, 1 ou 2	❒	❒
FEV cardiaque > 40 %.....	❒	❒
Clairance de la créatinine > 30 ml/min	❒	❒
Bilirubin < 2 UI et transaminases < 5 UI.....	❒	❒
Dyspnée stade 0, I, II (NYHA)	❒	❒
Index de comorbidité 0, 1, 2 ou 3.....	❒	❒
Femme n'étant pas enceinte ou allaitante	❒	❒

EVALUATION DE LA TAILLE DE LA RATE

	OUI	NON
La rate mesure plus de 20 cm d'axe maximal en imagerie au J60 post inclusion...	❒	❒
La rate n'a pas encore été mesurée en imagerie.....	❒	❒
Une splénectomie est programmée.....	❒	❒

Une date d'allogreffe a été fixée le [__][__] [__][__] [__][__]

FAXER au Secrétariat du GOELAMS
Fax: 02.47.37.35.12

Téléphone Secrétariat GOELAMS : 02.47.39 18 96
ou goelams@med.univ-tours.fr

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