

Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study
"HaploRescue"

INTERVENTIONAL RESEARCH PROTOCOL

Version N°1.2 of 20/09/2021

Project code number: APHP200129/ IDRCB No.:2021-A01409-32

- Coordinating Investigator: **Pr Régis Peffault de Latour**
Bone marrow transplantation Unit
Saint-Louis Hospital, Paris
Tel.: +33142385073
Email: regis.peffaultdelatour@aphp.fr
- Sponsor: AP-HP
and by delegation: Clinical Research and Innovation
Delegation (DRCI)
Hôpital Saint-Louis
DRCI head office project advisor: Fadela Ameral
Email: fadela.amerali@aphp.fr
- Methodologist: Unit for Clinical Research (URC)
GH Saint Louis Lariboisière, site Saint Louis
Clinical Research Unit project advisor:
Pr Sylvie Chevret
Tel. +33142499742
Email: sylvie.chevret@univ-paris-diderot.fr
- Entity responsible for monitoring the trial: Unit for Clinical Research (URC)
GH Saint Louis Lariboisière, site Saint Louis
Clinical Research Unit project advisor:
Pr Matthieu Resche-Rigon
Tel. +33142499742
Email: matthieu.resche-rigon@univ-paris-diderot.fr
DRCI-URC head office project advisor: **Fayrouz MARTINA**
Tel: +33 (0)1 42 38 53 25
Email: Fayrouz.Martina@aphp.fr
- Pharmaceutical coordination : Département Essais Cliniques (DEC)
Agence Générale des Equipements et Produits de Santé (AGEPS)
Dr. Blandine Lehmann
Sabrina Alessi
Kévin Cardet
Tel: +33 1 46 69 14 02

Clinical Research and Innovation Direction (DRCI)
Hôpital Saint Louis 75010 PARIS

INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

Research code number: APHP 200129

Title: Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study "HaploRescue"

Version N° 1.2 of: 20/09/2021

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

Coordinating Investigator:
Pr Régis Peffault de Latour
Bone marrow transplantation Unit
Saint-Louis Hospital, Paris

Date: ... 20/10/2021
Signature:

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

Date: ... 03/11/2021
Signature:

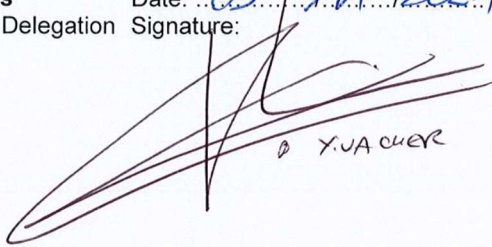

Y. VA CHEY

TABLE OF CONTENTS

1	SUMMARY	6
2	SCIENTIFIC JUSTIFICATION FOR THE TRIAL	10
2.1	HYPOTHESIS FOR THE STUDY	10
2.2	EXISTING KNOWLEDGE RELATING TO THE CONDITION UNDER INVESTIGATION	11
2.3	SUMMARY OF RELEVANT PRE-CLINICAL AND CLINICAL TRIALS	11
2.4	DESCRIPTION OF THE POPULATION OF TRIAL SUBJECTS AND JUSTIFICATION FOR THE CHOICE OF SUBJECTS	11
2.5	DESCRIPTION AND JUSTIFICATION OF THE DOSAGE, ROUTE OF ADMINISTRATION, ADMINISTRATION SCHEDULE AND TREATMENT DURATION	12
2.6	SUMMARY OF THE KNOWN AND FORESEEABLE BENEFITS AND RISKS FOR THE STUDY PARTICIPANTS	12
3	OBJECTIVES	13
3.1	PRIMARY OBJECTIVE	13
3.2	SECONDARY CLINICAL AND BIOLOGICAL OBJECTIVES	13
4	DESCRIPTION OF THE TRIAL	13
4.1	CONCISE DESCRIPTION OF THE PRIMARY AND SECONDARY ENDPOINTS	13
4.2	RESEARCH METHODOLOGY	14
4.3	SCREENING VISIT	14
4.4	BASELINE VISIT	14
4.5	FOLLOW-UP VISITS	15
4.6	EXPECTED LENGTH OF PARTICIPATION, CHRONOLOGY AND DURATION OF THE STUDY	16
4.7	TABLE OR DIAGRAM SUMMARISING THE CHRONOLOGY OF THE STUDY	17
4.8	DISTINCTION BETWEEN STANDARD CARE AND RESEARCH	19
4.9	TERMINATION AND EXIT RULES	20
5	ELIGIBILITY CRITERIA	21
5.1	INCLUSION CRITERIA	21
5.2	EXCLUSION CRITERIA	21
5.3	CLINICAL SELECTION AND INCLUSION CRITERIA OF A DONOR	22
5.4	EXCLUSION CRITERIA OF A DONOR	22
5.5	RECRUITMENT METHODS	22
6	TRANSPLANT PROCEDURE	23
6.1	TRANSPLANT MODALITIES	23
	CONDITIONING REGIMEN	23
	STEM CELL SOURCE	23
	GVHD PROPHYLAXIS	23
	PREVENTION OF EBV REACTIVATION	24
	INFECTION PROPHYLAXIS	24
6.2	AUTHORISED AND PROHIBITED TREATMENTS (MEDICINAL, NON-MEDICINAL, SURGICAL), INCLUDING EMERGENCY MEDICATIONS	24
6.3	MANAGEMENT OF RELAPSE	25
7	ADDITIONAL MEDICINAL PRODUCTS TO TRANSPLANT PROCEDURE SUPPLIED BY THE SPONSOR	25
7.1	RITUXIMAB	25
8	EFFICACY ASSESSMENT	26
8.1	DESCRIPTION OF PARAMETERS FOR ASSESSING EFFICACY ENDPOINTS	26

8.2	ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE EFFICACY DATA	27
9	SPECIFIC COMMITTEES FOR THE TRIAL.....	27
9.1	SCIENTIFIC STEERING COMMITTEE	27
9.2	DATA SAFETY MONITORING BOARD (DSMB)	27
10	SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY .	27
10.1	ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE SAFETY ENDPOINTS	27
10.2	RECORDING AND REPORTING ADVERSE EVENTS	27
11	DATA MANAGEMENT)	34
	DATA COLLECTION	34
11.1	IDENTIFICATION OF DATA RECORDED DIRECTLY IN THE CRFs WHICH WILL BE CONSIDERED AS SOURCE DATA	34
11.2	RIGHT TO ACCESS SOURCE DATA AND DOCUMENTS	34
11.3	DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA.....	35
11.4	OWNERSHIP OF THE DATA	35
12	STATISTICAL ASPECTS	35
12.1	PLANNED STATISTICAL METHODS, INCLUDING THE TIMETABLE FOR ANY PLANNED INTERIM ANALYSES.....	35
12.2	HYPOTHESES FOR CALCULATING THE REQUIRED NUMBER OF SUBJECTS, AND THE RESULT ...	36
12.3	STATE WHETHER SUBJECTS WHO EXIT THE STUDY PREMATURELY WILL BE REPLACED AND IN WHAT PROPORTION.	36
12.4	ANTICIPATED LEVEL OF STATISTICAL SIGNIFICANCE.....	36
12.5	STATISTICAL CRITERIA FOR TERMINATION OF THE STUDY.....	36
12.6	METHOD FOR TAKING INTO ACCOUNT MISSING, UNUSED OR INVALID DATA	36
12.7	MANAGEMENT OF MODIFICATIONS MADE TO THE ANALYSIS PLAN FOR THE INITIAL STRATEGY.....	37
13	QUALITY CONTROL AND ASSURANCE	37
13.1	GENERAL ORGANISATION	37
13.2	QUALITY CONTROL.....	37
13.3	CASE REPORT FORM	38
13.4	MANAGEMENT OF NON-COMPLIANCES	38
13.5	AUDITS/INSPECTIONS.....	38
13.6	PRINCIPAL INVESTIGATOR'S DECLARATION OF RESPONSIBILITY	39
14	ETHICAL AND LEGAL CONSIDERATIONS	39
14.1	METHODS FOR INFORMING AND OBTAINING CONSENT FROM THE RESEARCH PARTICIPANTS ..	39
14.2	PROHIBITION OF CONCOMITANT CLINICAL STUDIES PARTICIPATION AND EXCLUSION PERIOD AFTER THE TRIAL, IF APPLICABLE	40
14.3	LEGAL OBLIGATIONS.....	40
15	FUNDING AND INSURANCE	42
15.1	SOURCES OF FUNDING FOR THE TRIAL.....	42
15.2	INSURANCE	42
16	PUBLICATION	42
16.1	MENTION OF AP-HP AFFILIATION FOR PROJECTS SPONSORED BY AP-HP.....	42
16.2	MENTION OF THE SPONSOR AP-HP (DRCI) IN THE ACKNOWLEDGEMENTS OF THE TEXT	43
17	BIBLIOGRAPHY	43
17.1	LIST OF INVESTIGATORS.....	45
17.2	SERIOUS ADVERSE EVENTS REPORT FORM.....	46
17.3	PREGNANCY NOTIFICATION FORM	49
17.4	INCLUDE THE SCP	52

17.5	QUESTIONNAIRE OR SCALE.....	52
1-	QUALITY OF LIFE QUESTIONNAIRES	52
2-	SCALE	52
	CTC-AE -TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENT	52
	VERSION.....	52

1 SUMMARY

Full title	Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study
Acronym	HaploRescue
Coordinating Investigator	Pr Régis Peffault de Latour
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	<p>Prognosis of patients with graft failure is dismal, and re-transplantation is the sole option for long-term survival. Currently, there is no consensus concerning therapeutic options in patients with primary or secondary (within the 60 days post-transplantation) graft failure and finding a new donor within an acceptable delay is challenging. Literature is poor on the subject while the overall survival of such patients is about 30% at 1 year (1, 2). This situation thus represents today a very challenging unmet medical need.</p> <p>Recently, haploidentical (haplo) related donor Stem Cell Transplantation (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil (3). Our group re-transplanted a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT from her son using PTCy (5). We then retrospectively collected and analyzed data from 26 primary graft failure patients transplanted between 2011 and 2017 in 15 centers on behalf of French Society for Stem Cell Transplantation and Cell Therapy (SFGM-TC). The study population consisted mainly of patients with primary or secondary (within the 60 days post-transplantation) graft failure who underwent haplo-SCT and received PTCy as graft-versus-host-disease prophylaxis. The 1-year overall survival was about 60% suggesting that this approach might be a valid option in this particular poor clinical situation but now need validation through a phase II multicenter, national, prospective cohort study (4).</p>

Main objective and primary endpoint	<p>Main objective: To rescue patients with graft failure after a first allogeneic SCT (allo-SCT) using haplo-SCT with PTCy</p> <p>Primary endpoint: Overall Survival rate compared to an historical controls of 30% at 1 year.</p>
Secondary objectives and endpoints	<p>Secondary objectives:</p> <ul style="list-style-type: none"> - Graft failure, GvHD, progression free survival, relapse, non-relapse mortality - Interval between first allo-SCT and rescue haplo-SCT - Quality of life - Chimerism - Immune reconstitution <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> -Graft failure incidence. -Neutrophils and platelets engraftment at day 100 (3 consecutive days with neutrophils >0.5 G/L and 7 consecutive days with platelets >20 G/L). Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions. -Incidence of use of growth factors for poor hematopoietic reconstitution -Acute GvHD incidence at month 3 (M3) (date and maximum grading, first line treatment, response to steroids, treatment courses in case of steroid refractory GvHD. -Chronic GvHD incidence (date and grading at M24). -Relapse incidence at M12 and M24 -Progression free survival at M12 and M24 -Incidence of CMV and EBV infection at M12 -Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24 - Incidence and severity of VOD at M3 -Non-relapse mortality M24 -Incidence of cardiac toxicities at M12 -Overall survival at M24 -Interval between first allo-SCT and rescue haplo-SCT -Quality of life questionnaire (EORTC QLQ-C30- v3 for adults and PedsQL for minors) at inclusion, post-transplantation, M3, M6, M12, M24 only -Chimerism at M1, M3, M6, M12 -Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation -Iron overload estimation at M3, M6, M12 and M24
Design of the trial	Phase II multicenter, national, prospective cohort study
Population of trial subjects	Patients over 3 years old and all hematological diseases suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allogeneic hematopoietic stem cell transplantation (allo-SCT)

Inclusion criteria	<p>Patients:</p> <ul style="list-style-type: none"> -Aged from 3 to 70 years -All hematological diseases -Suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allo-SCT -With usual criteria for allo-SCT: <ul style="list-style-type: none"> • ECOG ≤ 2 • No severe and uncontrolled infection • Cardiac function compatible with high dose of cyclophosphamide • Adequate organ function: ASAT and ALAT $\leq 2.5N$, total bilirubin $\leq 2N$, creatinine clearance $\geq 30\text{ml / min}$ -With identification of a haploidentical donor (brother, sister, parents, adult children or cousin) -Absence of donor specific antibody (DSA) detected in the patient with a MFI ≥ 1500 (antibodies directed towards the distinct haplotype between donor and recipient) - With health insurance coverage (bénéficiaire ou ayant droit). - Understand informed consent or optimal treatment and follow-up. - Contraception methods must be prescribed during all the duration of the research. Women and men of childbearing age must use contraceptive methods within 12 months and 6 months after the last dose of cyclophosphamide, respectively. -Having signed a written informed consent (2 parents for patients aged less than 18) <p>NB: The authorized contraceptive methods are:</p> <ul style="list-style-type: none"> - For women of childbearing age and in absence of permanent sterilization: oral, intravaginal or transdermal combined hormonal contraception, oral, injectable or transdermal progestogen-only hormonal contraception, intrauterine hormonal-releasing system (IUS), sexual abstinence (need to be evaluated in relation to the duration of clinical trial and the preferred and usual lifestyle of the participants). - For man in absence of permanent sterilization: sexual abstinence, condoms
Exclusion criteria	<p>Patients:</p> <ul style="list-style-type: none"> - Aged < 3 years old and >70 years old - With uncontrolled infection - With Seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCV and associated hepatic cytolysis - Yellow fever vaccine within 2 months before transplantation

	<ul style="list-style-type: none"> - Cancer in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix) - Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50% - Heart failure according to NYHA (II or more) - Preexisting acute hemorrhagic cystitis - Renal failure with creatinine clearance < 30ml / min - Urinary tract obstruction - Pregnant (β-HCG positive) or breast-feeding - Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up - COVID vaccination or recent COVID disease <3 months - Tutorship or curatorship - Contraindications to treatments used during the research
Transplant modalities	<p>Conditioning regimen Fludarabine (30mg/m²/day from day -6 to day -4), Cyclophosphamide (14.5 mg/kg/day at day -6 and day -5) except for patients who received a total dose of Cyclophosphamide >100mg/Kg during the first Bone Marrow Transplantation Total Body Irradiation (2 Gray on day -1).</p> <p>Source of stem cell source Peripheral blood stem cell Minimal target dose of 4.10⁶ CD34+ cells/kg of recipient</p> <p>GvHD prophylaxis Cyclophosphamide 50 mg/Kg/day at D+3 and D+4 Ciclosporine from day+5 (residual 200 à 300ng/l) Mycophenolate mofetyl at 15mg/Kg x2/day from day+5</p> <p>Prevention of EBV reactivation Rituximab : 150mg/m² intravenously at Day+5 post Haplo-SCT Each infusion of Rituximab will be preceded by administration of anti-pyretic and an antihistaminic.</p>
Risks added by the trial	Risks are related to the SCT itself. Cardiac toxicities and hemorrhagic cystitis will be particularly monitored.
Scope of the trial	Primary or secondary (within the 60 days post-transplantation) graft failure is a rare but devastating condition after SCT. A recent strategy for haplo related donor transplantation, which has had some success, is transplantation of T-cell replete grafts with intensive immune suppression. Few retrospective non-controlled registry studies recently suggest that outcomes after haplo-SCT using PTCy approach might

	be superior to actual standard of care (i.e. retransplantation from an unrelated donor). Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients. This study might thus favor this strategy in case of primary or secondary (within the 60 days post-transplantation) graft failure after 1 st SCT.
Number of subjects included	For an objective of 31 patients to be allo-grafted, we anticipate 35 patients to include.
Number of sites	39 centres in France
Duration of the trial	Inclusion period: 36 months Participation period : 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.9 patient/centre (0,02 patient/month/centre)
Statistical analysis	Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals. Comparaison with the historical controls of 30% at 1 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011. Terminal analysis will be performed after the follow-up of the last included patient.
Sources of funding for the trial	<i>PHRC-K 2019</i>
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Hypothesis for the study

Prognosis of patients with graft failure is dismal, and re-transplantation is the sole option for long-term survival. Currently, there is no consensus concerning therapeutic options in patients with primary or secondary (within the 60 days post-transplantation) graft failure and finding a new donor within an acceptable delay is challenging. Literature is poor on the subject while the overall survival of such patients is about 30% at 1 year (1, 2). This situation thus represents today a very challenging unmet medical need.

Recently, haploidentical (haplo) related donor Stem Cell Transplantation (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil (3). Our group re-transplanted a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT from her son using PTCy (4). We then retrospectively collected and analyzed data from 26 primary graft failure patients transplanted between 2011 and 2017 in 15 centers on behalf of French Society for Stem Cell Transplantation and Cell Therapy (SFGM-TC). The study population consisted mainly of patients with primary or secondary (within the 60 days post-

transplantation) graft failure who underwent haplo-SCT and received PTCy as graft-versus-host-disease prophylaxis. The 1-year overall survival was about 60% suggesting that this approach might be a valid option in this particular poor clinical situation but now need validation through a phase II multicenter, national, prospective cohort study (5).

2.2 Existing knowledge relating to the condition under investigation

Primary or secondary (within the 60 days post-transplantation) graft failure is a rare but devastating condition after SCT. A recent strategy of haplo related donor transplantation with T-cell replete grafts and intensive immune suppression showed very encouraging results in this situation (4, 5). Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients (all biologic parents and children of a patient are haplo and each sibling has a 50% chance of being haplo). This study might thus offer a real curative strategy in this particular dramatic clinical situation.

2.3 Summary of relevant pre-clinical and clinical trials

Currently, there is no consensus concerning therapeutic options in patients with graft failure, and finding a new donor within an acceptable delay may be challenging. Cord blood, unrelated donors, or haploidentical transplantation are alternatives. However, the literature is scarce on the subject, and the long-term overall survival (OS) of retransplanted patients is estimated to be about 30% (1)

In the past years haploidentical transplantations with post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis have shown promising results in the treatment of many hematologic diseases, including some cases of graft failure (6)

In this context, we analysed data from 24 patients with graft failure or loss retransplanted with a haploidentical donor who received post-transplant cyclophosphamide (PTCy) as graft-versus-host disease prophylaxis (GVHD) (4). Fludarabine-based reduced-intensity conditioning was used in 23 patients and the Baltimore regimen in 14 patients. The median delay between previous and salvage transplantation for graft failure was 63 days (range, 39 to 98). In addition to PTCy, all patients received cyclosporine, and 22 patients also received mycophenolate mofetil for GVHD prophylaxis. With a median follow-up of 353 days (range, 16 to 2010), 1-year overall survival (OS) was 56% (95% confidence interval, 38% to 81%). Transplant complications accounted for 80% of deaths. The cumulative incidence of neutrophil engraftment at day +30 was 79%. Cumulative incidence of grades II to IV acute GVHD at day 100 was 14%, and 1-year cumulative incidence of chronic GVHD was 31%. One-year cumulative incidence of relapse was 13%. Stem cell source did not impact on engraftment, GVHD, relapse, or OS. Salvage haploidentical transplant with PTCy for rescuing graft failure patients leads to an acceptable 1-year OS and might be a valid option in this poor situation and justified to validate this therapeutic option through the actual phase 2 protocol "HaploRescue".

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

All hematological diseases will be concerned by this research. Indeed, the approach for patients with malignant or non malignant diseases is exactly the same in term of strategy for second HSCT in case of graft failure.

Patients aged less than 18 years old will be included in this study. Over the period 2016-2020, based on data from the PROMISE registry (European Bone Marrow Transplantation) where all consecutive hematopoietic stem cell transplantations are collected, 15 children in France with primary graft failure after their first Stem Cell

transplantation have received a second (rescue) haploidentical related donor Stem Cell Transplantation with cyclophosphamide post HSCT as graft-versus-host-disease prophylaxis. Only one death was registered so far with a median follow-up of 15 months. Those very positive results encourage us to propose “haplo-rescue” protocol to pediatric population too. Over the period 2016-2020, based on data from the PROMISE registry (European Bone Marrow Transplantation) where all consecutive hematopoietic stem cell transplantations are collected, 15 children in France with primary graft failure after their first Stem Cell transplantation have received a second (rescue) haploidentical related donor Stem Cell Transplantation with cyclophosphamide post HSCT as graft-versus-host-disease prophylaxis. Only one death was registered so far with a median follow-up of 15 months. Those very positive results encourage us to propose “haplo-rescue” protocol to pediatric population too.

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

The Baltimore group developed the PTCy strategy using haploidentical related donors with intra-venous injection at day +3 and day +4, using T-replete bone marrow in patients with advanced hematological malignancies (the so-called Baltimore protocole, reference 3). PTCy administered early at a fixed time point after bone marrow infusion, has shown to eradicate alloreactive donor and host T-cells, activated by respective antigens, thereby reducing the incidence of GVHD reaction (7). Details are indicated in section V.6.2 (“Transplant modalities”). We used this approach for a patient who experienced two consecutive graft failures and was successfully managed through a third haplo-SCT (5). The SFGM-TC retrospective study recently published was also using the Baltimore strategy (4). The difference with the Baltimore protocole is the choice to use Peripheral Blood Stem Cells (PBSC) as source of stem cells and not Bone Marrow (BM) to improve engraftment in this particular situation of graft failure and because more recent literature showed no difference in terms of outcomes using PBSC or BM in the context of a Baltimore approach (section 6.2 “Transplant modalities”). The other difference is the introduction of Rituximab 150mg/m² at Day+5 post HSCT to prevent the EBV reactivation (8). Indeed, EBV post transplant lymphoproliferative disorders (PTLD) is classical after alternative BMT. In a recent study using Cord Blood in patients with refractory aplastic anemia, the use of an early unique anti-CD20 injection (at day +5) was able to avoid EBV-associated lymphoproliferative disorder following BMT (9), illustrating the efficacy of an early anti-CD20 injection. EBV DNA monitoring, with early preemptive use of anti-CD20 in patients with increasing viral load will also help to prevent this type of complication (10).

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

Benefits will be evaluated in terms of efficacy to demonstrate a benefit in terms of Overall survival at one year using haplo-SCT with PTCy for rescuing patients with graft failure. Moreover, haplo-SCT with PTCy is a quick procedure, cheap, and available for almost all patients.

Risks are related to SCT itself. It is classical to estimate a higher risk of infections during second BMT because of intense immunosuppressive status. Patients will receive primary bacterial, viral and fungal prophylaxis to avoid as much as possible this risk.

PTCy will also be strictly followed in Haplorescue due to the known cardiac toxicity of cyclophosphamide and hemorrhagic cystitis related to its use in this situation. To avoid any excess of toxicity, we also decided not to use Cyclophosphamide in the conditioning regimen, for patients who received a total dose of Cyclophosphamide >100mg/Kg during the first Bone Marrow Transplantation.

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

12/57

3 OBJECTIVES

3.1 Primary objective

The main objective is to demonstrate a benefit in term of Overall Survival (OS) at one year using haplo-SCT with PTCy for rescuing patients with graft failure.

3.2 Secondary clinical and biological objectives

- Graft failure, GvHD, progression free survival, relapse, non-relapse mortality, OS
- Interval between first allo-SCT and rescue haplo-SCT
- Quality of life
- Chimerism
- Immune reconstitution

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

Primary endpoint

Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals (CI). Comparaison with the historical controls of 30% at 1 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011 (11).

Secondary endpoints

- Graft failure incidence.
- Neutrophils and platelets engraftment at day 100 (3 consecutive days with neutrophiles >0.5 G/L and 7 consecutive days with platelets >20 G/L). Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions. The use of growth factors for poor hematopoietic reconstitution
- Acute GvHD incidence at M3 (date and maximum grading, first line treatment, response to steroids, treatment courses in case of steroid refractory GvHD).
- Chronic GvHD incidence (date and grading at M24).
- Incidence and severity of VOD at M3
- Relapse incidence at M12 and M24 - Progression free survival at M12 and M24
- Incidence of CMV and EBV infection at M12
- Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24
- Non-relapse mortality M24
- Incidence of cardiac toxicities at M12
- Overall survival at M24
- Interval between first allo-SCT and rescue haplo-SCT
- Quality of life questionnaire (EORTC QLQ-C30- v3 for adults and Peds QL for minors)) at inclusion, post-transplantation, M3, M6, M12, M24 only for the adult population
- Chimerism at M1, M3, M6, M12,
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation
- Iron overload estimation at M3, M6, M12 and M24

4.2 Research methodology

Design of the trial

Phase II multicenter, prospective cohort study. 31 patients will receive a haplo-SCT.

Number of participating sites

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

Identification of the subjects

The subjects participating in this study will be identified as follows:

Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial

This reference number is unique and will be used for the entire duration of the trial.

4.3 Screening visit

The screening visit will take place within the 45 days prior to second haplo-SCT. The investigator will check the eligibility criteria and will propose the study to the patient. The transplant physician in charge of the patient will deliver informations about the protocol. Triplicated information and consent forms will be given to the patient by the investigator. No additional test or specific examinations are performed for research. The patient assessment is performed in the usual care of haplo-SCT.

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

	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
Patient or 2 parents for patients aged less than 18 years The "Non opposition" of the minor patient should be sought as soon as the minor is of age to understand	The transplant physician (investigator of research)	Screening visit	At the inclusion visit

4.4 Baseline visit

At this visit, the consent of the patient will be collected at the latest by D-10 before haplo-SCT. A Patient Information Sheet and consent form are given to the patient by the investigator; the investigator, and the third copy by the sponsor keep the original.

Baseline visit also consists in physical examination, biological testing and imagery. This assessment is performed according to the practice of the investigator. The donor's agreement is verified.

- **Physical examination**

- Reports of patient and disease history
- ECOG assessment
- Sorror score of comorbidities
- Complete physical examination with evaluation of tumor localization
- Electrocardiogram
- Echocardiogram with evaluation of left ventricular ejection
- Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking).
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)
- Liver ultrasound and doppler echography (baseline values)

- **Biological tests**

- Complete Blood count
- Prothrombin time (PT), Partial thromboplastin time (PTT)
- ABO and Rh typing Blood cell
- Chemistry panel (serum electrolytes with creatinine, calcium, glucose, uric acid, magnesium levels, ferritin, CRP)
- Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine)
- Circulating protein electrophoresis
- Pregnancy test (for women of childbearing age) before starting any treatment for conditioning regimen (D-6)*
- Haplo compatibility check between recipient and donor
- Search of anti-HLA antibodies with LUMINEX technology (DSA)
- Chimerism markers' identification

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

- **Infectious assessment**

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

- **Tumor assessment:**

- Pre-transplant disease evaluation
- Sinus and thorax CT scan

- **Imaging**

- Dental radiography
- Total body CT scan

- **Quality of life:** EORTC QLQ-C30- v3for adult patient and Peds QL for minors

4.5 Follow-up visits

Post- transplant monitoring

Patients are monitored daily during initial hospitalization to detect possible complications of procedure or GvHD occurrence. Once patients get out from the hospital, the follow-up will be done according to each center policy and protocol requirement but at least once a week until Months 3 and then in consultation on a regular basis lifelong.

The minimum expected length of hospitalization is 21 days.

The daily monitoring includes:

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

15/57

- Physical examination of the patient and safety assessment by collection of all adverse events/serious adverse events likely to occur as well as all actions taken because of these AEs. These AEs will be grading according to the CTC-AE scale.
 - Complete Blood count, chemistry assessment with kidney and liver test will be performed
 - Pregnancy tests (for women of childbearing age) at D+4 and D+35 and if MMF is continued after D+35 (in case of GVHD), a monthly pregnancy test will be performed until the end of MMF treatment
 - Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 will be performed weekly (or according to clinical context)
 - Grading of acute GvHD will be performed weekly during hospitalization and at each visit until J120
 - Cardiologic monitoring: Electrocardiogram will be checked before the infusion of cyclophosphamide and repeated in association to a dosage of troponine and proBNP on a daily basis for 3 consecutive days after the administration of cyclophosphamide and repeated after if any doubt. Weight measure will be done twice a day to identify quickly cardiac problems during 3 weeks then once a day until J120. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide (JACIE procedure).
- All adverse events (AEs) will be recorded. All AEs (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale. Acute GvHD shall be graded according to MAGIC CONSORTIUM 2016 (weekly during hospitalization and up to D120).
Chest X-ray (weekly until D100)
- Quality of life

Follow-up visits M1, M2, M3, M6, M12, M24.

- Clinical examination, blood cell count, chemistry panel with creatinine and liver test will be performed at each visit (routine follow-up).
- Disease evaluation will be performed at M3, M12, M24
- CD3/CD4/CD3/CD8/B lymphocytes/NK cells, protein electrophoresis and ferritin levels at M3, M6, M12 and M24
- Chimerism at M1, M3, M6, M12,
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 and toxoplasmosis at M1, M2, M3, M12.
- Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC) at J100
- Cardiac monitoring: a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M3, M12 and M24
- Safety assessment by collection of all adverse events/serious adverse events at each visit.
- Chronic GvHD and acute GvHD shall be graded as previously described
- Quality of life at M3, M6, M12, M24.

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

Maximum period between screening and enrolment	45 days
Length of Inclusion period	36 mois
Duration of participation for each subject	24 months

Total study duration:

60 months

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

4.7 Table or diagram summarising the chronology of the study

	Screening	Inclusion (baseline visit)	D0 = graft	Immediate post graft monitoring daily	M1	M2	M3	D100	M6	M12	M24
Patient (and or parents for minor) Information:	x										
Signature of the consent form ("non opposition" of the minor patient should be sought)		x									
Inclusion exclusion criteria check	x	X									
(&) β HCG test (before startany treatment for conditioning regimen))		D-6		D+4	D+35						
Sorrer comorbidities score		X									
Physical examination		X	X	x	X	X	X	X	x	X	x
Disease evaluation		x					x			X	X
Pre-transplant evaluation		X									
Lung function test		x						X			
Chest X-ray (weekly until D100)		x						x			
Dental radiography and Total body CT scan (baseline)		x									
Cardiac monitoring (a)		x		x (β)				X			X
Blood cell count		x	X	x	x	x	x	X	x	X	x
Chemistry panel with creatinine, liver test		x	X	x	x	x	x	X	X	X	x
(c) Aspergillus antigen, PCR for CMV, EBV, adenovirus, HHV-6			X	X	x	x	x		x	x	
Chimerism (b)		X					x			X	
Grading of acute GvHD				X	x	x	x				
CD3/CD4/ CD8/ / B lymphocytes (CD19) and NK cells(CD56), and protide electropheris , ferritin level		X			x		x		x	X	x
Quality of life questionnaire (EORTC QLQ-C30-V3 for adults, PedsQL for minors)		X		Post graft			x		X	x	x
Adverse events/serious adverse event All toxicity not attributed to GvHD will be classified according to CTC-AE toxicity, v5.0			X	X	X	X	X	X	x	X	x

& :The pregnancy tests before starting any treatment at D- 6, then at D+4 (MMF start at D+5) and D+35. If MMF is continued after D+35 (in case of GVHD), **a monthly pregnancy test will be performed until the end of MMF treatment.**

(a) Cardiology monitoring : Electrocardiogram and echocardiography at baseline visit for all the patient ,(β) : Only for haplo SCT group : Electrocardiogram will be checked before the infusion of cyclophosphamide and repeated in association to a dosage of troponine and proBNP on a daily basis for 3 consecutive days after the administration of cyclophosphamide. Weight measure will be done twice a day to identify quickly cardiac problems during 3 weeks then once a day until J120. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide. For all patients, a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at M3, M12 and M24.

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

(c) Weekly : Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6

4.8 Distinction between standard care and research

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

Procedures and treatments to be provided during the study	Procedures and treatments associated with standard of care	Treatments used outside its market authorization
Procedure/Treatments	Haploidentical SCT, conditioning regimen, GVHD and Infection prophylaxis, HSCT overall follow-up Rituximab Injection of donor lymphocyte (DLI) in case of relapse	Rituximab 150mg/m2 at Day+5 post HSCT
Hospitalizations *-Consultations		No
Imaging	Dental radiography Total Body CT scan	No

*The minimum expected length of hospitalization is 21 days.

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

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

For more information, the research related blood loss as a general rule should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time.

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

In the HaploRescue research, the biological follow up is identical to the current care in allograft.

4.9 Termination and exit rules

Criteria and procedures for prematurely terminating the study treatment

4.9.1 Different situations

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

The investigator must:

- o Document the reason(s)
- o Schedule further follow-up visits, especially in case of a serious adverse event.

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

- Subjects may exit the study at any time and for any reason.

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

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

The case report form must list the various reasons why the subject exited the study:

- Explicit withdrawal of consent
- Death
- Subject's personal reasons
- Lost to follow-up

Monitoring subjects after the premature termination of study

If a subject exits the trial before the end of study, this will in no way affect the standard care received for his/her condition.

Full or partial cancellation of the study

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

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

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

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

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients:

- Aged from 3 to 70 years older
- All hematological diseases
- Suffering from primary or secondary (within the 60 days post-transplantation) graft failure after a 1st allo-SCT
- With usual criteria for allo-SCT:
 - ECOG \leq 2
 - No severe and uncontrolled infection
 - Cardiac function compatible with high dose of cyclophosphamide
 - Adequate organ function: ASAT and ALAT \leq 2.5N, total bilirubin \leq 2N, creatinine clearance \geq 30ml / min
- With identification of a haploidentical donor (brother, sister, parents, adult children or cousin).
- Absence of donor specific antibody (DSA) detected in the patient with a MFI \geq 1500 (antibodies directed towards the distinct haplotype between donor and recipient).
- With health insurance coverage (bénéficiaire ou ayant droit).
- Understand informed consent or optimal treatment and follow-up.
- Contraception methods must be prescribed during all the duration of the research. Women and men of childbearing age must use contraceptive methods within 12 months and 6 months after the last dose of cyclophosphamide, respectively.
- Having signed a written informed consent (2 parents for patients aged less than 18).

NB: The authorized contraceptive methods are:

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

5.2 Exclusion criteria

Patients:

- Aged $<$ 3 years and $>$ 70 years
- With uncontrolled infection
- With seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCV and associated hepatic cytolysis
- Yellow fever vaccine within 2 months before transplantation
- Cancer in the last 5 years (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix)
- Uncontrolled coronary insufficiency, recent myocardial infarction $<$ 6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction $<$ 50%

- Heart failure according to NYHA (II or more)
- Preexisting acute hemorrhagic cystitis
- Renal failure with creatinine clearance ≤ 30 ml / min
- Urinary tract obstruction
- Pregnant (β -HCG positive) or breast-feeding
- Who have any debilitating medical or psychiatric illness, which preclude understanding the inform consent as well as optimal treatment and follow-up
- COVID vaccination or recent COVID disease <3 months
- Tutorship or curatorship
- Contraindications to treatments used during the research (see SmPC)*

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

5.3 Clinical selection and Inclusion criteria of a donor

The algorithm for the selection of a haploidentical donor has been define by the french society for stem cell transplantation (12, 13, 14).

- Intrafamilial donor having 1 HLA haplotype in common with the recipient
- Aged 18 to 70 years old. If no adult fulfills inclusion criteria, a minor donor may be chosen. In that case, the management of minor donors ≤ 18 years old will be done by a pediatrician, including the bone marrow harvest, and minor donors will give their assessment as the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.
- Presence of the usual clinical and biological criteria of eligibility of the donors of hematopoietic stem, including in particular the serological assessment authorizing the transplant. The management of the donor, before, during, and after the procedure, shall be done by a physician who is not in charge of the recipient. The follow-up of donors includes routine management and the management of collection-associated adverse events.
- No contraindication to administration of G-CSF

The modalities for mobilizing and collection of PBSC will be done according to JACIE accreditation.

5.4 Exclusion criteria of a donor

- Presence of donor specific antibody (DSA) with a MFI ≥ 1500 detected in the patient
- Pregnancy in the donor

5.5 Recruitment methods

The protocol is carried out by the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) (adult and pediatric centres). All members of SFGM-TC accepted to participate to this research (39 French sites).

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

Number of subjects/site	0.9
Number of subjects/site/month	0.03

In France, between 2014 and 2017, 134 patients received a second HSCT because of graft failure with 25 pediatric patients.

6 TRANSPLANT PROCEDURE

6.1 Transplant modalities

Before to start any treatments for conditioning regimen, a β HCG test will be done (see & 4.7). Transplantation modalities are following European guidelines (15).

Conditioning regimen

The conditioning regimen will be uniform in all patients, mainly immunosuppressive and not myeloablative since graft failure is characterized by hypocellular bone marrow and no need for anti-tumoral effect. It will consist of Fludarabine (30 mg/m²/day from day -6 to day -4), pre-transplant cyclophosphamide (14.5 mg/kg/day at day -6 and day -5) except for patients who received a total dose of Cyclophosphamide >100mg/kg during the first Bone Marrow Transplantation, and Total Body Irradiation (2 Gray on day -1).

Stem cell source

The stem cell source will be peripheral blood stem cell (PBSC), known to improve engraftment in this particular situation of high risk of rejection (16). This will allow achieving a high dose of infused CD34+ cells, correlated with better engraftment in patients with graft failure (17). Moreover, good results have been reported using PBSC instead of bone marrow in the context of bone marrow failure (18), a similar situation to graft failure.

G-CSF mobilized PBSC will thus be used. The donor will receive G-CSF from day-4 to day-1 subcutaneously (10 μ g/kg/day), with the minimal target dose of 4.10⁶ CD34+ cells/kg.

GVHD prophylaxis

- Cyclophosphamide 50 mg/kg/day at D+3 and D+4. The injection of cyclophosphamide will be accompanied by systematic injection of Mesna (Uromitexan®, 50 mg/kg) for the prevention of urinary toxicity. The dose of Mesna is twice that of cyclophosphamide divided in 4 injections per day of 30 minutes each. The first injection of Mesna is performed at the time of cyclophosphamide injection and then 3 hours, 6 hours and 9 hours after. Patients must not receive any immunosuppressive agents between the graft infusion and until day +5.

- Ciclosporine and Mycophenolate mofetil (MMF) from day+5

▪ Ciclosporine

3 mg/kg IV at D+5 (residual 200 à 300 ng/l) to start 24 hours after the last dose of cyclophosphamide

Ciclosporine will be injected intravenously over 24 hours or twice daily. When the oral route is possible, the treatment will be taken twice daily.

Ciclosporine is adapted to the renal function.

It is planned to stop the treatment:

- before J180 after a progressive withdrawal starting by 3 months post-SCT
- in case of renal failure (<30 ml/min) or thrombotic microangiopathy

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

▪ **MMF** at 15mg/kg x2/day IV or orally from day+5, to start 24 hours after the last dose of cyclophosphamide.

In absence of GvHD, MMF will be stopped between D35 and D45.

MMF will be stopped or decreased faster in case of unexpected prolonged cytopenias and in case of digestive disorders (diarrhea).

Prevention of EBV reactivation

All patients will receive 1 injection of an anti-CD20 monoclonal antibody (rituximab) (150 mg/m²) at Day+5 to prevent EBV reactivation.

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before administration of Rituximab.

Infection Prophylaxis

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

- Prevention of fungal infection by azols according to ECIL5, adapted to the SCT risk group (<https://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx>)
- Prevention of HHSV and VZV reactivation: aciclovir 250mg/m² x3/day IV then valaciclovir: 500 mg/day po.
- Prevention of toxoplasmosis reactivations and pneumocystis: Bactrim® 800 mg x3/week or atovaquone 750 mg x 2/day in case of cytopenias after engraftment
- Prevention of encapsulated bacteria: Oracilline® 50 000 UI/kg x 2/day
- Monthly polyvalent immunoglobulins if hypogammaglobulinemia (<4 g/L)

❖ Management of toxicities:

Antibiotics (aminosides, vancomycine), antivirals (Foscavir®), and antifungals (Ambisome®) will be adapted to the renal function. Voriconazole and posaconazole will be adapted to the hepatic function, Cymevan® to cytopenias. These adaptations will be regularly carried out in the transplantation department.

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

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

Authorized treatments

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

Treatments forbidden

Yellow fever vaccine is contraindicated.

Treatments not recommended

- For cyclophosphamide

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

24/57

- Attenuated vaccine (except yellow fever who is forbidden during 6 months after treatment discontinuation)
- Phenytoin
- Pentostatin
- For Fludarabine
- Pentostatin
- Dipyridamole or other inhibitor of adenoside captation

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

6.3 Management of relapse

Management of relapse is at the discretion of the investigator. However, if the injection of donor lymphocyte (DLI) is envisaged, the following procedures will be recommended: start with a dose of 1×10^6 CD3/kg, increasing by 0.5 log every 6 to 8 weeks up to 1×10^8 CD3/kg in the absence of GVH (according to the recommendations of the SFGM-TC).

7 ADDITIONAL MEDICINAL PRODUCTS TO TRANSPLANT PROCEDURE SUPPLIED BY THE SPONSOR

7.1 Rituximab

Posology for clinical trial: Rituximab will be given in one injection) (150 mg/m², 330 mg max at Day+5.

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

Supplies :

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

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

Dispensing:

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

Storage:

Treatments should be stored in the refrigerator (between + 2° C and + 8° C).

Keep the package in the outer carton in order to protect from light.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Administration:

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

The prepared Rituximab solution should be administered as an intravenous infusion through a dedicated line.

Rituximab should be administered under the close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.

Premedication consisting of an anti-pyretic and an antihistaminic, should always be given before each administration of Rituximab. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately.

Accountability and destruction: will be made by the CRA at the end of the study in the pharmacies.

A pharmacy manual will describe supplies, storage, dispensing, administration, accountability and destruction.

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

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

Progression-free survival

Progression-free survival (PFS) is defined as the time from graft until the occurrence of the following events: relapse (cytological) and death from any cause whichever comes first right.

Acute GvHD

Acute GvHD is defined according to MAGIC CONSORTIUM 2016 criteria (19). Each organ is rated with the diagnosis in stage, which define a grade. Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the period and maximum grade date. Histological documentation is recommended for GI GVHD.

Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 (20). The diagnosis of chronic GVHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:

A- Classical chronic GvHD in patients with only evidence of chronic GvHD

B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD

C- Late acute GvHD, which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

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

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

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

26/57

of organ	each						
-------------	------	--	--	--	--	--	--

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

The parameters for assessing efficacy were collected according to the schedule in table paragraph 4.8.

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific steering Committee

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

2. Missions:

The scientific steering committee will define the general organization and the conduct of the research. He will determine the initial methodology and oversee the trial.

He will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority

9.2 Data Safety Monitoring Board (DSMB)

See paragraph 10.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

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

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

The safety assessment shall be done by collecting all adverse events that occur during the research. All adverse event (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale (v5.0). Acute GvHD shall be graded according to MAGIC CONSORTIUM 2016 classification.

Adverse events shall be collected according to the schedule in table of paragraph 4.8 of the protocol.

10.2 Recording and reporting adverse events

Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

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

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

27/57

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

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

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

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

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..

For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.

Examples:

- a) any clinically significant increase in the frequency of an expected serious adverse reaction
- b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
- c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.

Examples:

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

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

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

Role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).

The investigator must **document** serious adverse events **as thorough as possible** and provide a definitive medical diagnosis, if possible.

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

28/57

The investigator must **assess the severity** of the adverse events by using:

- CTA-AE Toxicity Grading Scale, v5.0
- MAGIC CONSORTIUM 2016 classification for acute GvHD

The investigator must assess the **causal relationship** between the serious adverse events and the study procedures.

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

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

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

Table WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> · Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	<ul style="list-style-type: none"> · Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	<ul style="list-style-type: none"> · Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> · Event or laboratory test abnormality, with a time to drug intake ** that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

** Or study procedures

10.2.1.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see section 10.2.1.2.2.) and, if applicable, in the investigator's brochure as not requiring a notification without any delay.

A serious adverse event is any untoward medical occurrence that:

- | |
|--|
| <ol style="list-style-type: none"> 1- results in death 2- is life-threatening 3- requires inpatient hospitalisation or prolongation of existing hospitalisation 4- results in persistent or significant disability/incapacity 5- is a congenital anomaly/birth defect |
|--|

10.2.1.2 Specific features of the protocol

10.2.1.2.1 **Other events that require the investigator to notify the sponsor without delay**

- Adverse events judged as being "**medically significant**" (i.e. considered as "serious")
 - Non-engraftment
 - Bacterial, fungal viral and opportunist infectious complications (grade 3-4)
 - Veno-occlusive disease (moderate to severe)
 - Severe Thrombotic Microangiopathy
 - Idiopathic pneumonia (all stages)
 - Bronchiolitis obliterans (all stages)
 - Severe neurological disorders (coma, convulsion, encephalitis) occurring the first month post SCT
 - Cardiac toxicities (all stages) occurring in the first month post SCT
 - Overdose report
 - Infusion reactions, infections (grade 3-4) and heart-related problems related to cyclophosphamide
 - Severe dyspnoea, bronchospasm or hypoxia related to rituximab
 - Secondary neoplasia (excepted basal cell carcinoma of the skin or "in situ" carcinoma of the cervix).

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these serious adverse events, according to the same modalities and within the same timeline as mentioned above.

- **In utero** exposure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.

If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

The events are reported using a special form, appended to the protocol.

10.2.1.2.2 **Serious adverse events that do not require the investigator to notify the sponsor without delay**

These serious adverse events are simply recorded in the case report form. A CRF extraction of these serious adverse events will be performed for the DSMB meeting.

- **Normal and natural course of the condition:**

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

- **Special circumstances**

- Hospitalization for a pre-existing illness or condition

- Transfer to the emergency ward with self-limiting event or judged as not serious by the investigator.

- **Serious adverse events during the trial possibly related to the graft procedure realized as part of the patient's standard care (anti-infectious prophylaxis).**

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

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

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject begins treatment for the allograft
- throughout the whole follow-up period intended by the trial
- indefinitely, if the SAE is likely to be due to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities).

10.2.1.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized (de-identified). In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

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

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by e-mail (eig-vigilance.drc@aphp.fr) to the sponsor's safety department.

It is possible to send the SAE to the Safety department by fax to the sponsor's safety department, fax No. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail and in order to avoid duplicates.

For trials which use e-CRF:

- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by email;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the Safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

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

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation.

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form. If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.

The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.

If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

Role of the sponsor

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

10.2.1.5 Analysis and declaration of serious adverse events

The sponsor assesses:

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

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure, is considered unexpected.

The sponsor, acting through its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below.

- For serious adverse events likely to be related and considered expected to study procedures:
 - o refer to the Investigator's Brochure and to the SmPC for fludarabin, cyclophosphamide, uromitexan, ciclosporin, mycophenolate mofetil, rituximab and drugs used for premedication (reference to latest version available on <http://base-donnees-publique.medicaments.gouv.fr>).

- Reporting to the competent authority

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;

- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Note: the sponsor will report to the Agence de la Biomédecine (French health competent authority for biovigilance) and to the ANSM the unexpected adverse effects occurring in the donor and serious incidents without delay as soon as the sponsor becomes aware.

As a reminder, regarding this research, biovigilance applies for the donor. For patients treated in both groups, the vigilance of clinical trials applies.

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

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

10.2.1.6 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

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

10.2.1.7 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report which includes, in particular:

- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of inclusion of first patient.

Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).

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

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled. The DSMB's preliminary meeting should take place before the protocol submission to competent health authority (ANSM) and Ethics committee.

The members of the DSMB are:

Pr André Tichelli (Bâle, Suisse), Pr Jakob Passweg (Bâle, Suisse) and Dr Xavier Poiré (Louvain, Belgique). The DSMB's principle missions and their operating procedures are described in the DSMB chart of the clinical trial.

The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.

11 DATA MANAGEMENT

Data collection

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

11.2 Right to access source data and documents

11.2.1.1 Access to data

In accordance with GCP:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.

- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2.1.2 Source documents

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

11.2.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.

Under no circumstances will the names and addresses of the subjects be shown.

The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

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

The management and processing of the data will be done by the Centre de traitement de données INCA de l'APHP, Service de Diostatistique et Information Médicale (sDBIM), hôpital saint Louis, Paris (Pr. Sylvie Chevret).

Data entry

Data will be entered electronically via a web browser.

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

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

All personal data for this trial will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

11.4 Ownership of the data

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

12 STATISTICAL ASPECTS

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

Primary endpoint

Overall Survival will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals (CI). Comparaison with the historical controls of 30% at 1 year will be performed using the One-Sample Log-Rank Test proposed by Sun X et al in 2011 (11).

Secondary endpoints

- Graft failure incidence will be estimated with its 95% CI.
- Neutrophils and platelets engraftment incidence at day 100 (3 consecutive days with neutrophils >0.5 G/L and 7 consecutive days with platelets >20 G/L) will be estimated (with its 95% CI) using Gray's estimator considering death without Neutrophils and platelets engraftment respectively as competing risks.
- Absolute numbers of neutrophils and platelets at M1, M2, M3, M6 and M12, day of last platelet and red blood cell transfusions will be described using median and interquartile range
- Acute GvHD incidence at month 3 (M3) (date and maximum grading, first line treatment, response to steroids, treatment courses in case of steroid refractory GvHD) will be estimated (with its 95% CI) using Gray's estimator considering death without acute GvHD as competing risks.
- Chronic GvHD incidence (date and grading at M24) will be estimated (with its 95% CI) using Gray's estimator considering death without chronic GvHD as competing risks.
- Relapse incidence at M12 and M24 will be estimated (with its 95% CI) using Gray's estimator considering death without relapse as competing risks.
- Progression free survival at M12 and M24 (defined as the time between graft and relapse or death, whatever come first) will be estimated using the Kaplan-Maier's estimator with its 95% CI.
- Incidence of CMV and EBV infection at M12 will be estimated with its 95% CI.
- Severe infections (CTAE grade 3-4) à M3, M6, M12 and M24 will be estimated with its 95% CI.

- Non-relapse mortality M24 will be estimated (with its 95% CI) using Gray's estimator considering relapse as competing risks.
- Overall Survival at M24 will be estimated using the Kaplan-Maier's estimator with its 95% Confidences Intervals (CI).
- Incidence of cardiac toxicities at M12 will be estimated with its 95% CI.
- Quality of life questionnaire (EORTC QLQ-C30- v3-adults and Peds QL for minors)) at inclusion, post-transplantation, M3, M6, M12, M24 will be described using median and interquartile range
- Chimerism at M1, M3, M6, M12 will be estimated with its 95% CI
- Immune reconstitution by analyzing T, B, NK, regulatory T cell levels in the peripheral blood at M3, M6, M12 and M24 post-transplantation will be described using median and interquartile range
- Ferritin levels at M1 M3, M6, M12 will be described using median and interquartile range.

Characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categoriel characteristics).

All analyses will be performed in intention to treat.

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

A two-sided, one-sample logrank test calculated from a sample of 31 subjects achieves 90,3% power at a 0,05 significance level to detect a proportion surviving of 0,55 in the new group when the proportion surviving in the historic control group is 0,30. These proportions surviving are for a period of 12,0. Subjects are accrued for a period of 36,0. Follow-up continues for a period of 12,0 after the last subject is added. The probability that a subject experiences an event during the study is 0,74. The expected number of events during the study is 23. It is assumed that the survival time distributions of both groups are approximated reasonable well by the Weibull distribution with a shape parameter of 1,00 (21).

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

The analysis will be based on the intent-to-treat basis, that is, including all patients included and having received at least the conditioning for their graft. Only patient consent withdrawals with positive report of not using their data, if any, will be excluded.

12.4 Anticipated level of statistical significance

All tests will be two-sided with a type I error rate fixed at 0.05.

12.5 Statistical criteria for termination of the study.

Terminal analysis will be performed after the follow-up of the last included patient.

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

All the efforts will be done to avoid missing data in the outcomes.

Missing values for the main outcome measure are not expected to be observed; nevertheless, in case of occurrence, they will be handled using time-to-event methods in which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study using competing-risks estimates.

Missing values for predictors will be imputed using multiple imputation techniques based on chained equation, unless the rate of missing data is low, below 5% (in which case, only simple imputation based on the median value will be used).

All outliers will be checked carefully.

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

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

All modifications to the original protocol will be described in the SAP.

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

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

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

- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan. In practice, the centres will be opened with a priority for the centres that will have an eligible patient or within 3 months of the start of the research.

Scope of site monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level High.

13.2 Quality control

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

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

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

13.3 Case Report Form

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

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

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

13.4 Management of non-compliances

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

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

13.5 Audits/inspections

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

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

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

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

13.6 Principal Investigator's declaration of responsibility

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

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

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of 15 days is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Information of the holders of parental authority and their consent in the case of a study protocol involving a minor

In accordance with Article L.1122-2 of the Code de la santé publique (French Public Health Code), when an interventional study involving human participants is conducted on a non-emancipated minor, consent must be given by the holders of parental authority.

A reflection period of 15 days is given to those with parental authority between the time when they are informed and when they sign the consent form.

The freely-given written informed consent of the holders of parental authority is obtained by the investigator, or by a physician representing the investigator, before definitive inclusion of the minor in the study.

Information for minors participating in the research

Minors receive the information specified in Article L. 1122-1 of the *Code de la Santé Publique* (French Public Health Code), appropriate to their level of understanding, both from the investigator and from the holders of parental authority.

Minor's personal endorsement is sought regarding their participation in the study involving human participants. In any cases, the investigator cannot override their refusal or the revocation of their acceptance.

One copy of the signed and dated consent form is given to the holders of parental authority. The principal investigator or a physician representing him/her will keep one copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information recorded in the minor's medical file

The investigator will record the minor's participation in the clinical study in the minor's medical file, along with the procedure for informing and obtaining consent from the holders of parental authority as well as the procedure for informing the minor and a record of the minor's non-rejection to take part.

Special circumstances: the minor reaches the age of majority during his or her participation in the study

Minors who reach the age of majority during their participation in the study will be given new, relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

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

No exclusion period of participation after the participant has finished this study is defined in the context of this research.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies or in minimal risk and constraint study that does not involve therapeutic strategies, but this should be reported to the physician who follows it in the present research.

14.3 Legal obligations

The sponsor's role

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Development Department (DRCD) in order to conduct the "HAPLORESCUE" protocol, version 1.2 of 20/09/2021

study in accordance with Article L.1121-1 of the French Public Health Code. AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

Request for approval from the ANSM

AP-HP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

Declaration of compliance with the MR 001 "Reference Method" [include if applicable]

AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.

The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority's guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for **30 years** after the end of the trial.

This indexed archiving includes, in particular:

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

- the enrolment list or register
 - the appendices specific to the study
 - the final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

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

15.2 Insurance

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

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and name the sponsor AP-HP (DRCD) and the source of funding, if funded by a call for tenders (e.g. national PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming the sponsor and funders).

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

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

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

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

16.3 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC-K 2019 (French Ministry of Health)"

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

17 BIBLIOGRAPHY

- 1 Olsson R, Remberger M, Schaffer M, et al. Graft failure in the modern era of allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2013;48(4):537–43.
- 2 Ferra C, Sanz J, Diaz-Perez M-A, et al. Outcome of graft failure after allogeneic stem cell transplant: study of 89 patients. *Leuk Lymphoma.* 2015;56(3):656–62.
- 3 Luznik L, Donnell PVO, Symons HJ, et al. HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide. *Biol Blood Marrow Transpl.* 2008;14(6):641–50.
- 4 Prata PH, Resche-Rigon M, Blaise D et al. Outcomes of Salvage Haploidentical Transplant with Post-Transplant Cyclophosphamide for Rescuing Graft Failure Patients: a Report on Behalf of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant.* 2019 May 24. pii: S1083-8791(19)30324-6. doi: 10.1016/j.bbmt.2019.05.013. [Epub ahead of print].
- 5 Pagliuca S, Legendre H, Morin S, et al. Success of haploidentical hematopoietic stem cells transplantation in the treatment of graft failure. *Ann hemat.* 2016;95(2):353–54.
- 6 (Montoro J, Sanz J, Sanz GF, Sanz MA. Advances in haploidentical stem cell transplantation for hematologic malignancies. *Leuk Lymph.* 2016;57:1766–1775; Slade M, Fakhri B, Savani BN, Romee R. Halfway there: the past, present and future of haploidentical transplantation. *Bone Marrow Transplant.* 2016;52:1–6; Pagliuca S, Legendre H, Morin S, et al. Success of haploidentical hematopoietic stem cells transplantation in the treatment of graft failure. *Ann Hematol.* 2016;95:353–354).
- 7 Luznik L. Posttransplantation cyclophosphamide facilitates engraftment of major histocompatibility complex-identical allogeneic marrow in mice conditioned with low-dose total body irradiation. *Biology of blood and marrow transplantation. Journal of the American Society for Blood and Marrow Transplantation.* 2002;8(3):131-138.
- 8 In vivo B-cell depletion with rituximab for alternative donor hemopoietic SCT. Dominietto A, Tedone E, Soracco M, et al. *Bone Marrow Transplant.* 2012;47(1):101-106.
- 9 Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study. Peffault de Latour R et al. , *Blood* 2018Aug 16;132(7):750-754.
- 10 Blaes AH, Cao Q, Wagner JE, Young JA, Weisdorf DJ, Brunstein CG. Monitoring and preemptive rituximab therapy for Epstein-Barr virus reactivation after antithymocyte globulin containing nonmyeloablative conditioning for umbilical cord blood transplantation. *Biol Blood Marrow Transplant.* 2010;16(2):287-291).
- 11 Sun X, Peng P, Tu D. Phase II cancer clinical trials with a one-sample log-rank test and its corrections based on the Edgeworth expansion. *Contemp Clin Trials.* 2011 Jan;32(1):108-13. doi: 10.1016/j.cct.2010.09.009. Epub 2010 Oct 1.
- 12 Blaise, D. *et al.* Allogeneic stem cell transplantation from an HLA-haploidentical related donor: SFGM-TC recommendations (Part 1). *Pathol. Biol. (Paris)* 62, 180–184 (2014).
- 13 Nguyen, S. *et al.* Allogeneic stem cell transplantation from an HLA-haploidentical related donor: SFGM-TC recommendations (part 2). *Pathol. Biol. (Paris)* 62, 185–189 (2014).

- 14 Nguyen S, Chalandon Y, Lemarie C, Simon S, Masson D, Dhedin N, Suarez F, Renaud B, Charbonnier A, Yafour N, François S, Duléry R, Blaise D, Yakoub-Agha I, Rubio MT. Haploidentical hematopoietic stem cell transplantation: Guidelines from the Francophone society of marrow transplantation and cellular therapy (SFGM-TC). *Bull Cancer*. 2016 Nov;103(11S):S229-S242.
- 15 Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Duarte RF, Labopin M, Bader P, et al. *Bone Marrow Transplant*. *Bone Marrow Transplant*. 2019 Oct;54(10):1525-1552. doi: 10.1038/s41409-019-0516-2. Epub 2019 Apr 5.
- 16 Fuji S, Nakamura F, Hatanaka K, Taniguchi S, Sato M, Mori S, Sakamaki H, Yabe H, Miyamoto T, Kanamori H, Ueda Y, Kawa K, Kato K, Suzuki R, Atsuta Y, Tamaki T, Kanda Y. Peripheral blood as a preferable source of stem cells for salvage transplantation in patients with graft failure after cord blood transplantation: a retrospective analysis of the registry data of the Japanese Society for Hematopoietic Cell Transplantation. *BBMT* 2012;18(9):1407-14.
- 17 Chewning JH1, Castro-Malaspina H, Jakubowski A, Kernan NA, Papadopoulos EB, Small TN, Heller G, Hsu KC, Perales MA, van den Brink MR, Young JW, Prockop SE, Collins NH, O'Reilly RJ, Boulad F. Fludarabine-based conditioning secures engraftment of second hematopoietic stem cell allografts (HSCT) in the treatment of initial graft failure. *BBMT* 2007;13(11):1313-23.
- 18 Clay J, Kulasekararaj AG, Potter V, Grimaldi F, McLornan D, Raj K, de Lavallade H, Kenyon M, Pagliuca A, Mufti GJ, Marsh JC. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *BBMT*. 2014; 20(11):1711-6.
- 19 Harris AC et al..International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium, *Biol Blood Marrow Transplant*. 2016 Jan;22(1):4-10. doi: 10.1016/j.bbmt.2015.09.001. Epub 2015 Sep 16.
- 20 Filipovich AH, Weisdorf D, Pavletic S, et al. Diagnosis and staging working group report. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. *Biol Blood Marrow Transplant* 2005;11:945-56).
- 21 WU J. Sample size calculation for the one-sample log-rank test. *Pharm Stat*. 2015 Jan-Feb;14(1):26-33. doi: 10.1002/pst.1654. Epub 2014 Oct 22.

Dalle JH, Lucchini G, Balduzzi A, Ifversen M, Jahnukainen K, Macklon KT, Ahler A, Jarisch A, Ansari M, Beohou E, Bresters D, Corbacioglu S, Dalissier A, Diaz de Heredia Rubio C, Diesch T, Gibson B, Klingebiel T, Lankester A, Lawitschka A, Moffat R, Peters C, Poirot C, Saenger N, Sedlacek P, Trigos E, Vettenranta K, Wachowiak J, Willasch A, von Wolff M, Yaniv I, Yesilipek A, Bader P. State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) in Baden, Austria, 29–30 September 2015

List of addenda

17.1 List of Investigators

Centre	Adresse	IP	Mail
1	Saint-Louis	Peffault de Latour Régis	regis.peffaultdelatour@aphp.fr
2	CHU-Nancy	D'Aveni Maud	m.daveni-piney@chru-nancy.fr
3	Necker	Suarez Felipe	felipe.suarez@aphp.fr
4	CHU Besançon	Berceanu Ana	aberceanu@chu-besancon.fr
5	ICLN_Saint Priest En Jarez	Cornillon Jérôme	jerome.cornillon@icloire.fr
6	CHU Caen	Chantepie Sylvain	Chantepie-s@chu-caen.fr
7	CHU-Nantes	Garnier Alice	alice.garnier@chu-nantes.fr
8	CHU-Poitiers	Maillard Natacha	natacha.maillard@chu-poitiers.fr
9	Hôpital du Haut-Lévêque	Forcade Edouard	edouard.forcade@chu-bordeaux.fr
10	Saint-Antoine	Mohty Mohamad	Mohamad.mohty@inserm.fr
11	CHU-Grenoble	Bulabois Claude- Eric	CEBulabois@chu-grenoble.fr
12	CHU-Clermont	Bay Jacques Olivier	jobay@chu-clermontferrand.fr
13	Henri Mondor	Maury Sébastien	Sebastien.maury@aphp.fr
14	CHU-Nice	Loshi Michael	loschi.m@chu-nice.fr
15	Oncopole Toulouse	Huynh Anne	huynh.anne@iuct-oncopole.fr
16	CHU-Angers	Francois Sylvie	SyFrancois@chu-angers.fr
17	CHU-Rennes	Bernard Marc	marc.bernard@chu-rennes.fr
18	Hôpital Percy	Konopacki Johanna	Jokonopacki.hematopercy@gmail.com
19	CHU-Lyon sud	Barroco Fiorenza	fiorenza.barraco@chu-lyon.fr
20	Chru-Strasbourg	Lioure Bruno	Bruno.Lioure@chru-strasbourg.fr
21	CHU-Montpellier	Céballos Patrice	p-ceballos@chu-montpellier.fr
22	CAC_Rouen	Contentin Nathalie	nathalie.contentin@chb.unicancer.fr
23	Chu-amiens	Charbonnier Amandine	charbonnier.Amandine@chu-amiens.fr
24	Pitié-Salpêtrière	Nguyen-quoc Stéphanie	stephanie.nguyen-quoc@aphp.fr
25	Institut Paoli Calmette	Harbi Samia	harbis@ipc.unicancer.fr
26	Chu-limoges	Turlure Pascal	pascal.turlure@chu-limoges.fr
27	CHU Lille	Srour Micha	Micha.SROUR@CHRU-LILLE.FR
28	CHU-Lille	Bruno Bénédicte	Benedicte.bruno@CHRU-LILLE.FR
29	Robert-Debré	Dalle Jean Hugues	Jean-hugues.dalle@aphp.fr
30	CHU-Nantes	Rialland Fanny	Fanny.rialland@chu-nantes.fr
31	La Timone	Sterin Arthur	claire.galambrun@ap-hm.fr
32	CHU-Strasbourg	Paillard Catherine	Catherine.paillard@chru-strasbourg.fr
33	CHU-Estaing_Clermont Ferrand	Kanold Justyna	ikanold@chu-clermontferrand.fr

"HAPLORESCUE" protocol, version 1.2 of 20/09/2021

45/57

This document is the property of DRCI / AP-HP. All reproduction is strictly prohibited.

Version date: April 2018

34	IHOP, CHU Lyon	Renard Cécile	cecile.renard@ihope.fr
35	CHU Bordeaux	Jubert Charlotte	Charlotte.jubert@chu-bordeaux.fr
36	CHU-Montpellier	Sirvent Anne	a-sirvent@chu-montpellier.fr
37	CHU Rennes	Gandemer Virginie	virginie.gandemer@chu-rennes.fr
38	CHU de Nancy	Pochon Cécile	c.pochon@chru-nancy.fr
39	CHU de Rouen	Buchbinder, Nimrod	Nimrod.Buchbinder@chu-rouen.fr

17.2 Serious Adverse Events report form

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

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

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

Notification initiale

Suivi d'EIG N° du suivi |__|__|

1. Identification de la recherche	
Acronyme : HAPLO-RESCUE	Date de notification : __ __ __ __ 2 _0_ __ __ jj mm aaaa
Code de la Recherche : APHP 200129	Date de prise de connaissance de l'EIG par l'investigateur : __ __ __ __ 2 _0_ __ __ jj mm aaaa
Risque : D	
Titre complet de la recherche : Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide for rescuing patients with graft failure: a phase II study "HaploRescue"	

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

3. Identification et antécédents de la personne se prêtant à la recherche	
Référence de la personne : __ __ __ - __ __ __ __ - __ - __ <small>n°centre - n° ordre de sélection - initiale - initiale nom prénom</small>	Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
Sexe : <input type="checkbox"/> M <input type="checkbox"/> F	Date de naissance : __ __ __ __ __ __ __ __ jj mm aaaa
Poids : __ __ __ kg	Age : __ __ __ ans
Taille : __ __ __ cm	

Date de signature du consentement : _ _ _ _ 2_ 0_ _ _ jj mm aaaa
Date de la greffe : _ _ _ _ _ _ _ _ Ou non réalisée : <input type="checkbox"/> Conditionnement de la greffe : Conforme au protocole oui <input type="checkbox"/> non <input type="checkbox"/> Si non : indiquer la modification :	Prophylaxie de la GVHD : conforme au protocole: oui <input type="checkbox"/> non <input type="checkbox"/> Si non : indiquer la modification (notamment, doses, dates d'administration, raison)

4. Préparation de thérapie cellulaire/tissu/organe administré avant la survenue de l'évènement (barrer l'encadré si non applicable)					
Nom du produit expérimental	Voie (1) <i>(si applicable)</i>	Nombre de cellules administrées / Dose <i>(CNT/kg ou CD34+/kg) (</i>	Heure de début	En cours (2)	Heure de fin
Cellules Souches Périphériques	IV	_ _ _	_ _ hh _ _ min	<input type="checkbox"/>	_ _ hh _ _ min

5. Radiothérapie/médicaments de conditionnement/immunosuppresseurs/prophylaxie administrés avant la survenue de l'évènement indésirable NA <input type="checkbox"/>					
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie (1)	Posologie (préciser l'unité ex : mg/j)	Date de début (jj/mm/aaaa)	En cours (2)	Date de fin (jj/mm/aaaa)
			_ _ _ _ _ 2_ 0_ _ _	<input type="checkbox"/>	_ _ _ _ _ 2_ 0_ _ _
			_ _ _ _ _ 2_ 0_ _ _	<input type="checkbox"/>	_ _ _ _ _ 2_ 0_ _ _
			_ _ _ _ _ 2_ 0_ _ _	<input type="checkbox"/>	_ _ _ _ _ 2_ 0_ _ _

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

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'évènement indésirable (compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)							
⇒ Annexe jointe au présent formulaire : <input type="checkbox"/> Oui <input type="checkbox"/> Non							
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie ⁽¹⁾	Posologie (préciser l'unité ex : mg/j)	Dates d'administration (du jj/mm/aa au jj/mm/aa)	En cours (2)	Indication	Action prise	Causalité de l'EIG
			du _ _ _ _ _ _ au _ _ _ _ _ _	<input type="checkbox"/>		0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sait pas	0 : non lié au médicament 1 : lié au médicament 2 : ne sait pas
			du _ _ _ _ _ _ au _ _ _ _ _ _	<input type="checkbox"/>			

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

7. Evènement indésirable grave [EIG]	
Diagnostic : <input type="checkbox"/> Définitif <input type="checkbox"/> Provisoire	Organe(s) concerné(s) :
Date de survenue des premiers symptômes : _ _ _ _ _ _ 2_ 0_ _ _ _ Préciser lesquels :	

Non :

- à la progression de la maladie faisant l'objet de la recherche : (à compléter)
- à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :
- à une maladie intercurrente, laquelle :
- autre, préciser :

Notificateur

Investigateur

Tampon du service :

Nom et fonction :
Signature

Nom :
Signature

17.3 Pregnancy notification form

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

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

1. Identification de la recherche	Notification initiale <input type="checkbox"/> Suivi de notification <input type="checkbox"/> N° du suivi __ __	
Acronyme : HAPLO-RESCUE	Date de notification (initiale ou suivi) :	__ __ __ __ 2_ 0_ __ __ jj mm aaaa
Code de la Recherche : APHP 200129	Date de prise de connaissance de la grossesse par l'investigateur :	__ __ __ __ 2_ 0_ __ __ jj mm aaaa
Titre complet de la recherche : Haploidentical allogeneic hematopoietic stem cell transplantation with post-transplant cyclophosphamide in patients with acquired refractory aplastic anemia: a nationwide phase II study		
2. Identification du centre investigateur		
Nom de l'établissement :	Investigateur (nom/prénom) :	
Ville et code postal :	Tél :	
Service :		
3. Identification de la personne présentant une grossesse		
Référence de la personne : __ __ __ - __ __ __ __ - __ - __ <small>n°centre - n° ordre de sélection - initiale - initiale nom prénom</small>	Cas particulier d'une exposition paternelle : <input type="checkbox"/> Oui <input type="checkbox"/> Non	
Date de naissance : __ __ __ __ __	Référence de la personne : __ __ __ - __ __ __ __ - __ - __ <small>n°centre - n° ordre de sélection - initiale - initiale nom prénom</small>	
Date de signature du consentement: __ __ 2_ 0_ __ __	Date de naissance : __ __ __ __ __	
Date des dernières règles : __ __ 2_ 0_ __ __	Date de signature du consentement : __ __ 2_ 0_ __ __	
Et/ou date début de grossesse : __ __ 2_ 0_ __ __		
Expositions au cours de la grossesse :		
Tabac : <input type="checkbox"/> non <input type="checkbox"/> Oui (préciser nombre de paquets/année) :	<input type="checkbox"/> arrêt (préciser date) :	<input type="checkbox"/> poursuite
Alcool : <input type="checkbox"/> non <input type="checkbox"/> Oui (préciser unités OH) :	<input type="checkbox"/> arrêt (préciser date) :	<input type="checkbox"/> poursuite
Drogue : <input type="checkbox"/> non <input type="checkbox"/> Oui (préciser substance) :	<input type="checkbox"/> arrêt (préciser date) :	<input type="checkbox"/> poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux : _____ **Chirurgicaux :** _____

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

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

Date de la greffe : |_|_| |_|_| |_|_|_|_|_|_| Ou non réalisée :
Conditionnement de la greffe : conforme au protocole oui
 non, indiquer la modification :
Source de cellules : Moelle Osseuse : oui non
Nombre de cellules administrées : Conforme : oui non si non précise

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

	Date d'administration ou non administré	Voie	Posologie
Rituximab	_ _ _ _ _ _0_ _ _ ou <input type="checkbox"/> Non administré	IV mg/m2

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

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

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration ⁽¹⁾	Posologie / 24h
	_ _ _ _ _ _0_ _ _	_ _ _ _ _ _0_ _ _ <input type="checkbox"/> En cours		
	_ _ _ _ _ _0_ _ _	_ _ _ _ _ _0_ _ _ <input type="checkbox"/> En cours		
	_ _ _ _ _ _0_ _ _	_ _ _ _ _ _0_ _ _ <input type="checkbox"/> En cours		

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

9. Suivi de la grossesse

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

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

Date : |_|_| |_|_| |_|_0_|_|_| Terme : |_|_| SA |_|_| J

Fausse couche
→ Examen anatomo-pathologique disponible : Non Oui, précisez le résultat :
 Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : Non Oui, précisez le résultat :
 Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : Non Oui, précisez le résultat :
 Accouchement : Spontané Provoqué Voie basse Césarienne

Naissance multiple :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez le nombre :			
Souffrance fœtale :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :			
Mort-né :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :			
Placenta normal :	<input type="checkbox"/> Oui	<input type="checkbox"/> Non, précisez :			
Liquide amniotique :	<input type="checkbox"/> Clair	<input type="checkbox"/> Autre, précisez :			
Anesthésie :	<input type="checkbox"/> Générale	<input type="checkbox"/> Péridurale	<input type="checkbox"/> Rachianesthésie	<input type="checkbox"/> Aucune	
11. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)					
Sexe :	<input type="checkbox"/> Masculin	<input type="checkbox"/> Féminin			
Poids :	_ _ _ grammes	Taille :	_ _ _ cm	Périmètre crânien :	_ _ _ cm
APGAR : 1 minute :	_____	5 minutes :	_____	10 minutes :	_____
Malformation(s) congénitale(s) :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :			
Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :			
Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :	<input type="checkbox"/> Non applicable		
Notificateur	Investigateur	Tampon du service :			
Nom et fonction :	Nom :				
Signature :	Signature :				

17.4 Include the SCP

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

17.5 Questionnaire or scale

1-Quality of life questionnaires

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

2- Scale

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

version 5.0

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

Acute GVH according to MAGIC CONSORTIUM 2016

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

1. Stade par organe

Stade	Peau	Foie (bilirubine)	Tube digestif haut	Tube digestif bas (quantification des selles/jour)
0	Absence d'érythème cutané actif	< 2 mg/dl	Absence ou présence de manière intermittente de nausée, vomissement ou anorexie	< 500 ml/jour ou <3 selles/jour
1	Erythème maculopapulaire <25% SC	2–3 mg/dl	Présence de manière persistante de nausée, vomissement ou anorexie	500–999 ml/jour ou 3–4 selles/jour

2	Erythème maculopapulaire 25 – 50% SC	3.1–6 mg/dl	-	1000–1500 ml/jour ou 5–7 selles/jour
3	Erythème maculopapulaire > 50% SC	6.1–15 mg/dl	-	>1500 ml/jour Ou >7 selles/jour
4	Erythème généralisé (>50% SC) avec décollement (bulles) et desquamation > 5% SC	>15 mg/dl	-	Douleur abdominale importante avec ou sans ileus ou hémorragie digestive indépendamment du volume de selles

SC=surface corporelle

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

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

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

The diagnosis of chronic GVHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:

A- Classical chronic GvHD in patients with only evidence of chronic GvHD

B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD

C- Late acute GvHD, which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

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

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

of organ	each							
-------------	------	--	--	--	--	--	--	--

Manifestation de la GVHD chronique

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

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

Manifestation de GVHD chronique

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

- Peau** Erythème, sécheresse, prurit, changement de pigmentation (vitiligo, hyperpigmentation) plaques papulosquameuses, nodules, exfoliation, rash maculo-papulaire ou urticaire, sclérodermie, morphee (une ou plusieurs lésions lisses indurées et circonscrites)
- Ongles** Onychodystrophie, onycholyse, striés, fendus.
- Cheveux** Canitie prématurée (cuir chevelu, cils, sourcils), alopecie, amincissement du cuir chevelu, raréfaction de la pilosité corporelle.
- Bouche** Sécheresse, brûlures, gingivite, mucite, atrophie gingivale, érythème, lichen, ulcères, atrophie labiale, changement de pigmentation, contracture de la bouche, caries dentaires.
- Yeux** Sécheresse, brûlures, photophobie, douleur, larmoiement, sensation de grain de sable
- Organes** Sécheresse, sténose vaginale, dyspareunie, érythème vulvaire, atrophie **génétaux** génitale, lichen
- Foie** Élévation du bilan hépatique sanguin sans autre cause connue. En l'absence d'une autre atteinte organique, une biopsie est nécessaire pour confirmer le diagnostic.
- Poumons** Bronchiolite oblitérante, toux, sifflements, dyspnée d'effort, bronchites chroniques ou sinusites.
- Tube digestif** Anorexie, nausées, vomissements, perte de poids, diarrhées, dysphagie, malabsorption.
- Fasciite** Ankylose et réduction des mouvements, avec occasionnellement gonflement, douleurs, crampes, érythème et induration, atteignant le plus fréquemment les avant- bras les poignets et les mains, les chevilles, les jambes et les pieds, incapacité d'étendre les poignets sans fléchir les doigts ou les coudes, contractures.
- Muscles** Faiblesse proximale, crampes.
- Squelette** Arthralgies proximales des articulations des os du bassin, et parfois d'articulation moins importantes
- Séreuses** Douleurs pulmonaires ou cardiaques secondaires à une pleurésie ou une péricardite.

Gradation de GVHD chronique par organe:

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

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