ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Full Title: " ***Treatment of refractory systemic lupus erythematosus by injection of allogeneic mesenchymal stem cells derived from the umbilical cord***"

Acronym: « MSC SLE »

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MTI-PP FOR HUMAN USE

Version N°6.0 of 28/07/2021

Project code number: P150302J/EUDRACT No: 2017-001 400-29

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

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The study was approved by the Ethic committee (CPP) of Nord Ouest III on 16/03/2018 and authorised by the ANSM on 29/01/2018.

Tableau de suivi réglementaire des modifications du protocole de la recherche

	N° de version et date	Date de l'avis favorable CPP	Date de l'Autorisation ANSM	Description de la MS/commentaires
Protocole	**V1.2 12/03/2018 Cons CPP + ANSM**	**16/03/2019** V 1.2 du 12/03/2018	**29/01/2018** V 1.2 du 12/03/2018	**NA**
Modification substantielle n°1	**V2.0 du 03/06/2019**	**07/09/2019**	**26/07/2019**	- Modificatiions portant sur les éléments suivants : le protocole, la NIFC et la BI (tel que décrit dans le formulaire de demande de modification substantielle n°1 qui suit cette demande) : - Actualisation de la brochure investigateur : la version 2.0 du 03/06/2019 remplace la version 1.1 du 25/08/2017. - Uniformisation des différents documents - Ajout d'un score d'évaluation de la comorbidité - Adaptation de volume de prélèvements sanguins - Changement de la chef de projet DRCI (promoteur) en charge de cette Recherche - Suppression du typage HLA et microchimérisme qui ne seront pas effectués - Mise à jour RGPD des documents - Mise à jour des formulaires de notification EIG et grossesse et ajout d'une nouvelle feuille de traçabilité - Ajout d'un EIG à déclarer et modification des EIG à notifier sans délai au promoteur
Modification substantielle n°2	**V2.0 du 03/06/2019**	**07/09/2019 V2.0 du 03/06/2019**	**03/09/2019 V2.0 du 03/06/2019**	- Pour protocole, NIFC et BI, dans les critères d'inclusions : Elargissement des critères d'inclusion en remplaçant > par ≥ pour les doses des immunosuppresseurs - Pour protocole, NIFC et BI, dans les critères d'exclusions : Ajout de la PCR en optionnel pour les critères d'exclusion virologiques - Pour protocole, NIFC et BI : pour les examens biologiques : Précisions sur le bilan infectieux (sérologie)
Modification substantielle n°3	**V3.0 du 18/07/2019**	**07/11/2020 V3.0 du 18/07/2019**	**10/01/2020 V3.0 du 18/07/2019**	Modifications portant sur les documents suivants : IMPD et certificat de conformité du nouveau lysat plaquettaire : ***Le site fabricant du produit fini***

				(modification effective à partir de mars 2020). La prorogation de l'autorisation d'activité MTI-PP n°ETI/14/O/008 de l'Unité de Thérapie Cellulaire, Hôpital Saint-Louis arrivant à échéance le 12 mars 2020, la fabrication du produit fini sera assurée à partir de cette date par le centre Meary de production de MTI-expérimentaux, Hôpital Saint-Louis, dont le dossier d'autorisation est en cours d'instruction par l'ANSM. Le transfert de la production sur le centre Meary se fera seulement après l'obtention de l'autorisation de l'ANSM. ***- Le changement de référence/fournisseur d'une matière première critique entrant dans le procédé de fabrication du produit fini.*** Suite à un arrêt de commercialisation de la référence de lysat plaquettaire humain Stemulate® (référence PL-SP-SB-100 de Cook Regentec), un changement de référence/fournisseur de lysat plaquettaire est nécessaire. Le lysat plaquettaire qui sera utilisé en remplacement sera le MultiPL'100i® (référence BC0190032 de Macopharma). Le changement de référence du lysat plaquettaire ne concerne que la fabrication du produit fini sur le site fabricant de l'Hôpital Saint-Louis, Paris (Unité de Thérapie Cellulaire puis Plateforme MTI-Meary). Le stock des poches de la substance active nécessaire à la réalisation de l'essai clinique a déjà été produit par le site fabricant Centre for Cell Gene & Tissue Therapeutics, Royal Free Hospital, London avec le Stemulate® selon le dossier initial autorisé par les autorités. Le changement de référence est notifié tableau 11 page 24-25 du DME V3.0 du 28/11/2019 mentionnant l'ensemble des matières premières entrant dans le procédé de fabrication du produit fini. L'utilisation MultiPL'100i® nécessite l'ajout dans le milieu de culture d'héparine sodique, contrairement au Stemulate®. Le changement de référence a fait l'objet d'une validation du procédé de fabrication du produit fini. Les données sont présentées dans le tableau 14 page 29 du DME. Les résultats sont comparables à ceux obtenues lors de l'autorisation

				initiale avec l'utilisation du Stemulate® et sont conformes aux spécifications. Une étude de stabilité du produit fini a également été effectuée et montre une stabilité conforme sur une durée de 4 heures (tableau 19 page 34). Le certificat de conformité du MultiPL'100i® (du lot ayant été utilisé pour la validation) est joint à la demande d'autorisation de modification substantielle ainsi qu'en annexe du DME v3.0 du 28/11/2019 (évaluation de la sécurité virale page 36). Le MultiPL'100i® est produit par Macopharma en France à partir d'un pool de donneurs allemands qualifiés. Le lysat plaquettaire fait l'objet d'une viro-inactivation par gamma-irradiation à une dose minimale de 39.0kGy, validée en accord avec la Pharmacopée Européenne. Macopharma fournit un certificat de conformité pour chaque lot de lysat plaquettaire comprenant l'origine et la qualification des donneurs, le certificat d'irradiation et le certificat d'analyse.
Modification Substantielle n°4	**V4.1 du 08/01/2021**	**22/01/2021 V4.1 du 08/01/2021**	**03/02/2021 V4.1 du 08/01/2021**	Mise à jour des analyses du laboratoire SITI de Rennes dans le protocole (critères d'inclusion, objectifs secondaires et critères d'évaluation secondaires) et l'annexe 5 du protocole et dans la NIFC : o Nombre de tubes pour le dosage des cytokines et l'immunophénotypage o Mise à jour des volumes des tubes o Changement des tubes EDTA en tubes héparinés o Précision « Lithium sans gel » pour les tubes héparinés o Suppression du dosage des cytokines et de la RNAthèque à M6 et M12 : il ne nous apparaît pas nécessaire d'effectuer ce dosage aux vues des données de littérature sur l'efficacité à court terme des MSC. o Ajout d'un objectif secondaire prévu initialement dans le protocole : analyse de l'immunogénicité des MSC à M0, M1 et M3. o Ajout d'un critère d'évaluation secondaire par l'étude des anticorps anti-HLA pour l'analyse de l'immunogénicité des MSC à M0, M1 et M3 : analyse par « crossmatch ». Mise à jour annuelle de la Brochure Investigateur et conformément à la modification substantielle n°3 Remplacement du Technicien d'Etudes Cliniques du service de Médecine Interne, Maladies Auto-Immunes et Pathologie Vasculaire du protocole : Mr Catney Charles est remplacé par Mme Eola Francius.

				Mise à jour des documents du circuit du MTI-PP concernant le changement de site du fabricant du produit fini (modification effective à partir de mars 2020) conformément à la demande de modification substantielle n°3 et validée : étiquettes, notice d'injection, certificat de validation du produit, fiche de libération et fiche de prescription. Ajout de l'affiche de diffusion pour les patients. Mise à jour l'affiche de diffusion pour les médecins.
Modification Substantielle n°5	**V5.0 du 25/06/2021**		**07/07/2021** **V5.0 du 25/06/2021**	Prolongation des inclusions de 18 mois soit jusqu'au 18/03/2023 et du suivi des patients jusqu'au 18/03/2024 Changement du chef de projet DRCI, Elodie Lemadre est remplacée par Damien Vanhoye Changement de la coordinatrice d'études cliniques : Chafia Abbou est remplacée par Marine Cognat
Modification Substantielle n°6	**V6.0 du 28/07/2021**			Les membres du CSI en accord avec le secteur vigilance ont mis en avant l'importance du suivi des évènements thrombotiques. Cette mesure urgente de sécurité sera suivie d'une modification substentielle du protocole afin d'intégrer le suivi des évènements thromboemboliques dans le protocole comme évènements médicalement significatifs.

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1 SUMMARY

Full title	**Treatment of severe refractory systemic lupus erythematosus by injection of allogeneic mesenchymal stem cells derived from the umbilical cord**
Acronym	MSC-SLE
Coordinating Investigator	Professor Dominique FARGE-BANCEL Internal Medicine : Auto-Immune Diseases and Vascular Pathology, UF 04 Hôpital St-Louis 1, avenue Claude Vellefaux, Paris 75010 Paris
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Systemic Lupus Erythematosus (SLE) is a rare (prevalence: 40- 50/100 000 persons) heterogeneous auto-immune and auto-inflammatory Disease (AD), affecting both sexes and all races, with a peak incidence / prevalence among black people and a predilection for women in the 3rd-4th decade of life. SLE is characterized by successive periods of flares and remission, which may all vary in duration and quality. Prognosis of severe forms of SLE, which affect lung, heart or brain in addition to renal involvement, has improved, but still evolution remains pejorative in a subset of patients whose 10 years mortality remains 10-15%, even in tertiary referral centers. For 20 years, no new prospective clinical trial in the course of SLE has demonstrated its effectiveness. New biological therapies have not yet made the long awaited breakthrough in the treatment of severe SLE and only anti-Blys monocolonal antibody has gained indication in moderately active SLE. In addition, serious adverse side effects (progressive multifocal Leukoencephalopathy) observed with several biologics in AD patients has dampened their expected benefits. For SLE subjects resistant to 1er or 2nd line conventional treatment, there is a need to develop more effective therapies with fewer long term side effects, based on new immunomodulatory and immunosuppressive strategies. According to their in vitro immunomodulatory properties and ability to induce tissue repair mechanisms, Mesenchymal Stem cells (MSC) have been proposed as a new therapy for several AD, including SLE. The use of allogeneic umbilical cord-derived MSC is based on experimental and human clinical data, particularly produced by Nanjing team (Pr Sun) in China. It is also logical to select SLE patients with the same severity criteria as those used worldwide to validate the efficacy of anti-Blys therapies. Similarly, the analysis of the expected results should take into account criteria similar or comparable to those used for the pivotal clinical trials. This trial is a unique opportunity to set up collaboration between Saint-Louis APHP, clinical expert center for cell therapy in AD, and University College London for cell manufacturing.

Main objective and primary endpoint	Main objective: To assess the tolerance of allogeneic umbilical cord derived MSC administration for severe SLE refractory to standard therapies (cyclophosphamide mycophenolate mofetil and corticosteroids with or without anti CD20) Primary endpoint: Immediate tolerance as assessed during the first injection and 10 days after the allogeneic MSC injection, according to standards CTCAE side effects.
Secondary objectives and endpoints	Secondary objectives : 1- Feasibility of allogeneic UC-MSC administration in the treatment of severe SLE subjects refractory to conventional therapies 2- Tolerance three months after injection, considering the observed morbidity and the overall survival in SLE treated subjects until 1 year after the procedure. 3- Analysis of biological and clinical response on routine clinical and biological examination and criteria for monitoring lupus using SELENA SLEDAI-, BILAG, SF36, EQ5D, SRI, SLICC-SLE scores. 4- Analysis of the efficacy at 3-months after injection of allogeneic UC-MSCs according to the proportion of subjects with Major Clinical Response (RCM). 5- Percentage of subjects with Partial Clinical Response (CPR) during the 12 months of follow-up study. 6- Evaluation of the immunomodulatory effect of MSC by : a- Routine laboratory criteria, including immunophenotyping, every 3 months during the follow-up period b- Analysis of specific cytokine production at M0, M1 and M3. 7- Analysis of MSC immunogenicity at M0, M1 and M3 Secondary endpoints : 1) Safety Tolerance will be assessed during the injection and within the first 10 days following the MSC injection, at M1, M3, M6 and M12 according to side effects defined by CTCAE standards (Miller Results of cancer treatment Cancer 1981; 47 (1): 207 - 214). Treatment-related toxicity will be analyzed according to the international World Health Organization (WHO) (maximum degree of toxic attacks by the body). An injection will be considered as not tolerated for any toxicity criteria above grade ≥ 3. 2) Proportion of subjects with Major Clinical Response (MCR) and the proportion of subjects with Partial Response Clinic (PCR) during the 12 months of study follow-up at 3, 6, 9 and 12 months (M3, M6, M9 and M12). 3) Disease activity measured by the BILAG scores (0 and 72) and SELENA-SLEDAI (0 to 105) every 3 months, as compared to inclusion, until the end of the follow-up period (M3, M6, M9 and M12). 4) SRI response rate, measured every three months (M3, M6, M9 and M12) during follow-up: a SRI response is defined as a 4 points reduction of SELENA SLEDAI-score, no new BILAG A score for an organ and no more than one new BILAG B score and no worsening (increase of 0.3) in the overall evaluation of the physician as compared to inclusion values. 5) Presence of comorbidities according SCLICC-SLE index at M0 and every three months during study follow-up (M3, M6, M9 and M12) ; and Charlson Comorbidity Index at eligibility.

	6) Quality of life assessed by the Short Form 36 version 2 (SF-36v2) and EQ5D before injection and every 3 months until the end of the monitoring period (M3, M6, M9 and M12), and at M1. 7) Percentage of subjects with an average dose of prednisone reduced by 25% compared to M0 and who will be <7.5 mg / day for weeks 40 to 52. The average daily corticosteroid dose will be measured every 3 months until the end of the monitoring period (MO, M3, M6, M9 and M12). 8) The number of treatment failure defined by one of the following: - end stage renal disease requiring dialysis or transplantation - sustained doubled creatinine value from the two lowest values observed between screening and baseline and confirmed four weeks later. - active lupus nephritis attributed to active SLE as defined by either of the two criteria: i. a doubling value of proteinuria: proteinuria> 1 g / 24 hours for the subjects who were <0.5 g / 24 hours at baseline or proteinuria> 2 g / 24 hours for the subjects who were> 1g / 24 hours at baseline ii. nephropathy with a 25% increase in serum creatinine with respect to the value at baseline and simultaneously having a value of proteinuria doubled up at least 2 g / 24 hours, hematuria (two positive urine test strips) and the presence Cell cylinders. These two criteria must be confirmed twice at 2-week intervals. - need for steroid therapy intravenously, plasmapheresis, immunoglobulin IV or other immunosuppressive therapy to treat aggravation of SLE. 9) Standard Immunological and biological markers, including lymphocytes immuno-phenotyping: complete blood count, creatinine, proteinuria 24h, autoantibodies (anti-DNA antibodies and native ANAS), complement system C3, C4 and CH50, immunophenotyping, at M0, M1 and every three months during the follow-up period of the study (M3, M6, M9 and M12). 10) Specific cytokines production at M0, M1, M3 after inclusion. 11) Analysis of MSC immunogenicity at M0, M1 and M3, according to: - anti-HLA antibodies dosage - cross-match analysis
Design of the trial	Single center phase I-II open study with national recruitment within the FAI2R network
Population of trial subjects	SLE active subjects refractory to prior standard therapies
Inclusion criteria	Patient : **1-** Age > 18 years and < 70 years. **2-** Diagnosis of Systemic Lupus Erythematosus (SLE) according to the ACR criteria with positive antinuclear antibodies. **3-** Subjects with sustained disease activity defined by a SELENA-SLEDAI SLE activity index ≥ 6 at baseline, **4-** Inefficacy or adverse effects necessitating discontinuation of first and second line therapies of SLE including: a. Prednisone orally ≥ 6 mg / day (or equivalent) for at least 28 days. b. At least one or more of the following immunosuppressive therapies for 3 months in total:

	i- Cyclophosphamide, iv bolus ≥500 mg / month for 3 months minimum ii- Mycophenolate mofetil, orally or equivalent at a dose≥ 2000 mg / day for at least 90 days iii- Azathioprine orally at a dose≥ 2 mg / kg / day for at least 90 days; iv- Methotrexate orally or parenterally, at doses ≥ 20mg / week for at least 90 days; v- Leflunomide orally, at a dose of≥ 10-mg / day for at least 90 days; vi- Rituximab (anti-CD20) intravenous bolus 375 mg / m2, once a week for four weeks or total dose of 1 g twice a day for two weeks vii- Cyclosporine orally, at a dose of 2.5-5 mg / kg / day, for at least 90 days; viii- Belimumab intravenously or subcutaneous at monthly bolus of 10 mg / kg infusion), for at least 3 months. **5-** Patient who received treatment of SLE at stable doses for a minimum of 30 days prior to eligibility, including one of the following treatments: prednisone (or equivalent) alone or combined with antimalarial treatment, an anti-inflammatory steroidal and / or an immunosuppressant. **6-** Negative pregnancy test for women of childbearing age. **7-** For men and women : Using effective contraceptive methods during treatment and within 3 months after the end of treatment for men with her partner of childbearing age **8-** Signed Informed Consent. **9-** Affiliation to social security.

Exclusion criteria	Subjects: **1-** Pregnancy, breastfeeding or lack of appropriate contraception during study duration **2-** Presence of: a) Renal failure: calculated creatinine clearance of <30 ml / min b) Cardiac failure: clinical signs of congestive heart failure; left ventricular ejection fraction <40% on echocardiography; uncontrolled ventricular arrhythmia; c) Hepatitis defined by abnormal levels of transaminases (AST, ALT> 2 x normal) not related to disease activity. d) Respiratory disease: mean PAP> 50 mmHg (echocardiography), respiratory failure defined by a resting blood pressure of oxygen at PaO 2 < 70 mmHg and / or PaCO2 > 50 mmHg without oxygen **3-** Severe psychiatric disorders, including severe psychosis related to SLE, which would prevent to give informed consent or to undergo the procedure. **4-** Active neoplasia or concomitant myelodysplasia, except for basal cell carcinoma or squamous cell carcinoma or in situ cervix carcinoma. **5-** Bone marrow failure defined by neutropenia $<0.5.10^9$/L, thrombocytopenia <30. 10^9 / L, anemia < 8 g / dL, lymphopenia CD4 + <200 x 106 / L caused by another disease than SLE. **6-** Acute or chronic uncontrolled infection: HIV 1/2, HTLV-1/2, Hepatitis B (HBs Ag surface antigen), Hepatitis C with positive PCR (optional PCR) **7-** Patient having received belimumab intravenously or subcutaneous within 2 months of Baseline, or having received rituximab or other B cell depleting biologic therapy within 6 months of Baseline **8-** Current substance abuse or recent (within 60 days) history of substance abuse **9-** Patient in periods of exclusion from the national roster of researchers **10-** Patient with Linguistic or psychological incapacity to sign informed consent **11-** Patient already included in another study at the same time. **12-** Poor patient compliance. Patient under legal protection.
Investigational medicinal product(s)	Phase I-II, Allogeneic Umbilical Cord derived-MSCs injected by slow intravenous infusion according to the weight of the recipient and patient groups in the study, at doses of: - 1.10^6 CSM / kg - 2.10^6 CSM / kg - 4.10^6 CSM / kg 1 injection during 30min to 1h by Intravenous infusion,
Comparator treatment	NA
Interventions added for the trial	NA
Risks added by the trial	Risks level D

Scope of the trial	The immunosuppressive and / or immunomodulatory action of allogeneic MSCs (from umbilical cords of a healthy donor) will allow beneficial action on patients with severe SLE resistant to conventional treatments.
Number of subjects included	10 patients
Number of sites	Monocentric (St Louis Hospital)
Duration of the trial	Inclusion period: 42 months Participation period (treatment+follow-up): 12 months Total duration: 54 months
Number of enrolments expected per site and per month	0,2 inclusion per month, per site
Statistical analysis	Initially 5 subjects at the initial dose of 2.10^6 CSM/kg recipient weight will be included. The following 5 subjects will be enrolled in a dose: - 1.10^6 MS /kg there is a high probability of excessive toxicity* at 2.10^6 MSC / kg; - 4.10^6 CSM/kg if there is a low probability of excessive toxicity* 2.10^6 CSM / kg **The toxicity criteria are described in CTCAE classification* Each patient cohort will be scanned in a sequential Bayesian approach to estimate the probability of toxicity to the administered dose allowing an adaptation of the function of the toxicity observed in the dose previous subjects.
Sources of funding for the trial	"Subvention de recherche Thérapie génique et cellulaire en néphrologie"(Subv.Thérapie génique FdR-AFM_AIRG 2014) funding by « Fondation du Rein and l'Association Française contre les Myopathies (AFM Téléthon) », in collaboration with « l'AIRG France" and DRCI (sponsor AP-HP)
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC BACKGROUND FOR THE TRIAL

2.1 Introduction

Stromal cells were initially identified in the bone marrow by Friedenstein in 1976 [1], as a "fibroblast-like" cell population able to differentiate in the osteogenic pathway and initially described as bone cells precursors. Subsequent studies showed that these cells differentiation capacities extend to other mesodermal cells lineages: namely to the chondrocytes, the adipocytes and the muscle cells [2]. In 1991, on the basis of such differentiation capacity into multiple cell lineages, Caplan [3] introduced the name of "mesenchymal stem cells (MSCS)", although many terms have been used to describe this non-homogeneous population of multipotent cells. Among the various stem cells types, the MSC can relatively easily be isolated from either adult or cord tissues, cultured in vitro and such MSC population appears promising for human clinical application.

The MSC are part of the highly specialized microenvironment, where they participate in the regulation of hematopoietic stem cells (HSC) self-renewal and differentiation [4]. At the BM level, the interaction between stromal mesenchymal cells and hematopoietic progenitors is illustrated by the influence of the MSC on the early differentiation and B-cell lymphopoiesis. There is a close interaction between the BM stromal cells and the development of B-cell progenitors which, in response to cytokines synthesis (interleukin 7, stem cell factor (SCF), Flt3 ligand, thymic stroma lymphopoietin (TSL) and stromal (SDF) cells-derived factor) express the pre B (pre B cell receptor) surface marker. This marker is essential to the survival, the proliferation or the differentiation and the allelic exclusion of pre B cell [5]. Thus, MSC directly support the hematopoietic cells within the BM.

The understanding of MSC immunoregulatory properties was primarily focused on their ability to inhibit the proliferation of T lymphocytes. Since then, numerous studies have shown that the MSC affect the function and the differentiation of several other types of immunocompetent cells [6-9]. These biological data led to the first human clinical studies to evaluate the efficacy of MSC in treating graft-versus-host disease [10]. MSC immunoregulatory and immunosuppressive properties also constitute an experimental rational for the use of MSC to treat several autoimmune diseases.

2.2 Hypothesis for the study

The immunosuppressive and / or immunomodulatory effects of allogenic umbilical cord derived-MSCs will be well tolerated and will allow to improve clinical spectrum severe SLE patients resistant to prior conventional treatments

2.3 Existing knowledge relating to the condition under investigation

2.3.1 Systemic Lupus Erythematosus (SLE)

General information

SLE, as defined according to the ACR criteria [11, 12] is a rare, heterogeneous and systemic, inflammatory and AD with a prevalence of 40 to 50/100 000 persons. It affects both sexes and all races, with a peak incidence / prevalence among black people and a predilection for women in the 3rd to 4th decade of life. Its exact origin is still unknown, although heredity, environment and hormonal factors are involved. Most patients are women (> 85%) with a higher frequency in certain ethnic groups, especially among black people. The clinical picture is highly polymorphic and may include dermatological, rheumatological, renal, neurological, psychiatric, pleural and/or pericardial symptoms. The biological hallmark of SLE is the presence of antinuclear factors (FAN), anti-DNA double-stranded and/or anti-nucleosome antibodies, and a decline in serum complements levels [12, 13]. SLE is characterized by successive periods of flares and remission, which may all vary in duration and quality. Biological monitoring includes regular search for proteinuria, and repeated dosage of anti-dsDNA antibodies, and complement. The reappearance of immunological abnormalities (in particular anti-dsDNA antibodies) after a period of normalization may predict clinical disease exacerbation. These successions of flares may lead to renal failure requiring sometimes dialysis. Prognosis of serious and rare severe forms of SLE which affect lung, heart or brain in addition to renal involvement has improved in recent decades due to early diagnosis and treatment with immunosuppressive drugs combined with better control of hypertensive and infectious complications. However, there is still a subset of patients whose evolution remains pejorative, so that even in tertiary referral centers, the 10 years mortality remains 10% [14]. Therefore there is a need to develop more effective treatments for the most severe SLE patients, using

new immunosuppressive and immunomodulatory approaches, preferably with fewer long term side effects. There is also a need to reduce premature mortality associated with rapidly progressive atherosclerosis in SLE since, despite an apparent reasonable pressure control, sustained infra clinical inflammatory disease promotes the development of endothelial lesions and plaque formation [15-19]. In addition prolonged exposure to corticosteroids and various immunosuppressive drugs enhance the induced morbidity beyond damages related to SLE disease per se.

Pathophysiology

Lupus is characterized by abnormal B lymphocyte tolerance resulting in the production of anti-nuclear autoantibodies specifically directed against native DNA and nucleosome. Innate immunity and T cells play a role in the dysregulation of the B cells response and infiltrate the target tissues, causing subsequent damage. B and T lymphocytes immune cells cooperate to produce pathogenic autoantibodies. SLE physiopathology is complex, involving both genetics, epigenetics, hormonal and environmental predisposing factors, the activation of pro-inflammatory dendritic cells (DCs) (innate immunity) and the stimulation of inflammatory cells CD4 T and B cells (adaptive immunity) in the production of pathogenic autoantibodies and of a wide range of inflammatory cytokines (including type 1 IFN) [20].

The role of innate immunity may be associated with a disruption of two cells types: the DCs and the neutrophils. Although the exact mechanism remains to be elucidated, the DCs may play a key role in the expansion of T cells and of autoreactive B cells with the production of auto-antibodies, indicating their role in the promotion of the extra follicular humoral response in SLE patients. Dysregulation of neutrophil extracellular traps (NETS) is another important SLE pathophysiological component. SLE activated neutrophils die in a unique process called “NETosis”, which results in the release of large amount of structured free DNA, an important source of autoantigens, which are then captured by the DCs leading to their activation and subsequent production of pathogenic type I IFN.
The function of autoreactive B and T cells is better understood. Tolerance of B lymphocytes is abnormal, which, in combination with the activation of the B cell receptors, including Toll-like receptors and other activation factors of B cells, can promote the activation and survival of autoreactive B cells.

2.3.2 SLE Treatment

First line induction treatment of SLE, aiming to induce remission in the first 6 to 9 months of disease onset rely on oral steroids (above 0.5 mg/kg/day progressively tapered below 20 mg/day) in combination with either cyclophosphamide or mycophenolate mofetil, based on the NIH protocols and the Euro lupus protocols with 15 yrs follow-up. The current initial standard therapy for active BILAG A SLE relies on either the: a) cyclophosphamide (CY), according to the standard NIH treatment with 0.75 g/m^2/month x 6 iv cyclophosphamide [21-23], b) the short term Eurolupus protocol at doses lower than the NIH on a shorter duration with the same efficiency and less toxicity (CY regimen of 6 x 500 mg iv cyclophosphamide at 2 weeks interval) [24, 25]; or c) mycophenolate mofetil at 2 g daily for 3 to 6 months with a good efficiency and variable tolerance [26-30]. Other monoclonal antibodies directed against the T cell or B cell receptors and adhesion molecules involved in T and B cells interactions [31] and their co-stimulation signals, such as an anti-CD20 rituximab [32-38] and other monoclonal antibodies against IFN gamma [39] CD40 [40] or anti BLYS can be used [41, 42]. Only the Belimumab - the first new drug approved in Europe for the treatment of the SLE in 56 years has shown its effectiveness in moderate forms as an induction after two randomized trials of

phase III [41, 43-46]. Because rituximab allowed to obtain remission following rapid B cell depletion, with complete to partial early response rates close to 100%, although relapse occurred in approximately 60% of the cases it has progressively emerged as the third line therapy for induction of remission in cases of SLE resistant to standard treatment with azathioprine or mycophenolate mofetil as maintenance therapy as recommended by the National French health care program (https://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/ald_21_lap_lupus_web.pdf).. Rituximab binds to the B-cell specific antigen CD20, and depletes B cells from the peripheral blood and lymphoid tissues, with a strong rationale for its use in treating SLE. While being explored simultaneously in a number of other autoimmune diseases, rituximab has been tested in small series of patients with life-threatening refractory SLE and in SLE central-nervous-system symptoms, allowing to consistently report "striking improvement with excellent tolerability and high efficacy" in many patients. The variability in the individual responses is not yet fully understood and observations of multifocal leuco-encephalopathy questioned the risk of JC virus infection in SLE patients which is yet impossible to quantify. Despite the large number of patients included over the past decade in several randomized trials compared to placebo, none has demonstrated the efficacy of rituximab. Nonetheless, rituximab is very often used off-label as third line treatment for induction of remission in SLE cases resistant to standard treatment, as underlined by recent French national consensus guidelines for use of biotherapies in lupus (In the process of submission : "International and multidisciplinary expert recommendations for the use of biologics in systemic lupus erythematosus";"Kleimann JF, Tubach F, Le Guern V, Mathian A, Richez C, Saadoun D, Sacre K, Sellam J, Seror R, Amoura Z, Andres E, Audia S, Bader-Meunier B, Blaison G, Bonnotte B, Cacoub P, Caillard S, Chiche L, Chosidow O, Costedoat-Chalumeau N, Daien C, Daugas E, Derdèche N, Doria A, Fain O, Fakhouri F, Farge D, Gabay C, Guillo S, Hachulla E, Hajjaj-Hassouni N, Hamidou M, Houssiau F, Jourde-Chiche N, Koné-Paut I, Ladjouz-Rezig A, Lambotte O, Lipsker D, Mariette X, Martin-Silva N, Martin T, Maurier F, Meckenstock R, Mékinian A, Meyer O, Mohamed S, Morel J, Moulin b, Mulleman D, Papo T, Poindron V, Puéchal X, Punzi L, Quartier P, Sailler L, Smail A, Soubrier M, Sparsa A, Tazi-Mezalek Z, Leith Z, Zuily S, Sibilia J, Gottenberg JE; on behalf of the CRI (Club Rhumatismes et inflammations); FLEUR (Réseau Français du Lupus), IMIDIATE (Immune-Mediated Inflammatory Disease Alliance for Translational and Clinical Research) and FAI2R (Filière Nationale des Maladies Auto-Immunes et Auto-Inflammatoires Rares) networks."). For these reasons, and following international specific advice [47] we have decided to leave the choice to patients and investigators to use rituximab therapy prior to inclusion, but this is not a prerequisite in the proposed trial.

2.3.3 Maintenance Treatment for SLE.

Once induction therapy has allowed disease control, maintenance therapy is based on the lowest dose of steroids in combination with an anti-metabolite, such as azathioprine or mycophenolate mofetil for steroid sparing effects, in association with antimalarial drugs such as hydroxychloroquine [48]. The response to induction therapy as well as the number of relapses during maintenance treatment [24, 49] are important determinant of long term SLE disease evolution. Response ranges rates to induction therapy vary from 20 to 100% at 6 months according to the definition of response or improvement, the extent of visceral involvement, the ethnic origin and the socio-economic profile. Among the subjects with active SLE treated with this regimen, overall approximately 20 % (10 to 36%) fail to respond, 50% (10 to 65%) will relapse after initial treatment, 5 to 15 % will evolve towards end stage disease and 10% to 15 % will die at 10 years. There are still subgroups of patients with severe or recurrent active forms of SLE that in tertiary referral centers, still shows altered prognosis with high morbidity and 10% mortality at 10 years. The mortality rates among all SLE subjects is 4

times high compared to healthy individuals. In the USA, the survival rate drops to 95% at 5 years and 78% at 20 years, with similar data in other regions, such as Latin America, Greece and Saudi Arabia [14, 15, 50]. Most of these subjects have initial severe pulmonary renal or cerebral SLE disease. In a cohort analysis of 207 subjects with long term follow-up, the overall survival rates at 5, 10 and 15 years were 96%, 93% and 76% respectively [14]. One third of the 17 deaths results from active disease manifestations, predominantly in men with severe initial form of SLE, low response to initial treatment, sometimes favored by poor compliance. Other causes of deaths namely infections, gastrointestinal bleeding or cancer were related to SLE disease or its treatment. Therefore, despite better control of SLE with the use of cytotoxic and/or immunosuppressive agents associated with high-dose prednisone, initial severe forms of the disease are still important factors of adverse long-term survival. Despite the plethora of single biologics now available in clinical trials, none of them except the anti-Blys antibody has demonstrated lasting effect.

Unlike other systemic AD, new biological therapies have not yet made the long awaited breakthrough in the treatment of severe SLE. In addition, the occurrence of short terms serious adverse side effects recently observed (progressive multifocal Leukoencephalopathy and reactivation of JC virus) after the use of monoclonal agents in non HIV Crohn's disease patients [51, 52] has dampened the benefit expected benefits from use of biotherapies. In summary, there is a need to develop more effective therapies with fewer long term side effects, based on new immunomodulatory and immunosuppressive strategies for SLEsubjects resistant to 1er or 2nd line conventional treatment.

In this context, the use of allogeneic umbilical cord-derived MSC is based on both experimental and human clinical data, particularly produced by Nanjing (Pr Sun) in China. For 20 years, no new prospective clinical trial in the course of the SLE has demonstrated its effectiveness except recently the use of antibodies anti-Blys [41, 44-46, 53]. It is also logical to select SLE patients with the same severity criteria as those used worldwide to validate the efficacy of anti-Blys therapies. Similarly, the analysis of the expected results should take in account criteria similar or comparable to those used for the pivotal clinical trials. This trial is a unique opportunity to set up collaboration between Saint-Louis Hospital (AP-HP), clinical expert center for cell therapy in AD where the trial was conceived (Pr Farge), and University College London (Pr Lowdell). Allogeneic umbilical cord derived-MSCs will be produced in Good Manufacturing Practices conditions by UCL (Pr Lowdell) and provided to Saint-Louis Hospital (AP-HP) for the final product release at Cell Therapy Unit (CTU) (Dr Cras, Pr Larghero) and administration in selected patients (UF04, Pr Farge).

2.3.4 Mesenchymal Stem Cells and immunomodulation: in vitro data.

MSC and T cells

The first *in vitro* data demonstrating that MSC inhibit the T lymphocytes activation and proliferation derive from studies with human [6, 54, 55], non-human primate [56] or rodents [57] BM derived MSC. In *Vitro*, MSC obtained from healthy BM do not induce T cells proliferation in a unidirectional mixed lymphocyte reaction (MLR), even after treatment by interferon [55]. Added as a third party, MSC inhibit MLR and this inhibition persisted when the MSC were introduced late during the MLR. This effect was observed regardless of the MSC origin: identical to the recipient, to the donor or from a third party. Therefore, there is no immunological restriction on their capacity to inhibit T lymphocyte proliferation. This inhibition concerns both CD4+ and CD8+, as well as T naive and memory T cells [57]. The MSC inhibitory effect depends on the dose of MSC introduced in the MLR.

The exact molecular mechanisms responsible for MSC immunosuppressive properties in vitro are still to be specified. Inhibition of T cell proliferation by MSC requires the production of inflammatory cytokines such as IFN-gamma by T lymphocyte [58]. Moreover, the inhibition of T cells proliferation appears as the consequence of cellular communications mediated by the release of soluble factors synthesized by each cell population [59]. The production of soluble factors, in particular Transforming Growth Factor (TGF) beta 1 [60], prostaglandin E2 (PGE2), HLA-G [61] and indoleamine 2,3-dioxygenase (IDO) which inhibits the T lymphocytes proliferation by degradation of tryptophan in toxic metabolites [61], are proposed mechanism to explain the MSC immunosuppressive effects. The role of IDO in the inhibition of proliferation was questioned. Gieseke et al. [62] demonstrated that the MSC inhibitory effects on T cells were beyond the IDO expression and the signaling *via* receptor of the IFN - γ1. In vitro data reported by Wang D et al [63] show that allogeneic Umbilical Cord derived MSC inhibit the proliferation of T suppressive cells in SLE subjects by secreting large amounts of IDO. The authors also demonstrate that the abundant secretion of interferon γ (IFN γ) by CD8 + T cells in SLE subjects is one of the key factors to increase the activity of IDO by allogeneic MSC and this mechanism involves the IFNγR1/JAK2/STAT signaling pathway. T-cell anergy induced by the MSC is another hypothesis, since the MSC are not expressing the co-stimulatory molecules, such as CD80 and CD86 [55]. Several studies have shown that lack of response of T lymphocytes in the presence of MSC was transient and could be restored after the MSC have been removed from the culture [6-10, 54-57]. However, the results may differ between species since it has been shown, in mice, that MSC could induce T cell tolerance [64]. The MSC could act via inhibition of the activated T cells divisions even after the addition of exogenous IL-2 [65]. The observed differences between studies may be related to experimental conditions but also to the human (normal or pathological subjects) or murine origin of MSC. Finally, the MSC are able to modulate the immune response by inducing a population of regulatory T (Treg) cells. MSC induce the CD8+ Treg, which are responsible for the inhibition of lymphocyte proliferation in an allogeneic context [66]. An increase in the population of CD4 + CD25 + FoxP3 + has been demonstrated in cultures of lymphocytes stimulated in the presence of MSC [67, 68].

Other results contribute to explain the mechanism by which the MSC exert their immunosuppressive capacity [69]. First, it was demonstrated that inhibition of T cell proliferation was dependent on INF - γ and at least on one of the three following cytokines: TNF-alpha, IL-1alpha or IL-1beta synthetized by T lymphocytes. This combination of cytokines induces the expression by the MSC of high levels of chemokines and of inducible Nitric Oxide Synthase (iNOS). Chemokines will then induce the cells migration near to the MSC and at the same time, the lymphocyte proliferation is inhibited by nitric oxide. Moreover, in a mouse model, the injection of MSC not expressing the iNOS does not prevent GVHD, unlike the injection of normal MSC [69]. The action of pro-inflammatory cytokines during the immunosuppression induced by the MSC is linked to the action of chemokines and nitric oxide.

MSC and B cells

The first studies in murine models showed that the MSC were capable of inhibiting the proliferation of B lymphocytes stimulated by an anti-CD40L and IL-4 [65] or pockweed [70]. In both situations, the mechanisms inducing B cells inhibition involve physical contact between the MSC and the B cells and the synthesis of soluble factors by the MSC. In a BXSB lupus mice model, Deng and al [71] showed that allogeneic MSC were able to inhibit the proliferation, activation and secretion of IgG by B lymphocytes. The same authors showed that, in a MLR/lpr Lupus mouse treated by bone marrow derived MSC, the inhibition of B cell functions (proliferation, differentiation, and secretion of antibodies) depends on CCL2, a metalloprotease [72]. In humans, Corcione and al.[7] showed that the MSC inhibit the proliferation and activation

of B cells when stimulated with anti-IgG antibodies, the soluble CD40L and cytokines (IL-2 and IL-4) and modulate their differentiation, the antibodies production and chemotaxis. The inhibition of B cells functions is dependent on soluble factors released by the MSC. Conversely, other teams only showed a reduction of the B cells proliferation in the presence of IFN-gamma [58].

MSC and NK cells

Several studies showed that the MSC were capable of inhibiting NK cells proliferation of as induced by IL-2 or IL-15 as well as the production of IFN gamma [8]. The effect of MSC on the NK cells -mediated cytotoxicity is still debated. No cell lysis inhibition was observed when freshly isolated NK cells were tested for their ability to kill allogeneic HLA class I positive or negative targets in the presence of MSC [8]. Conversely, NK cells grown for 4 to 5 days with IL-2, in the presence of MSC, showed reduced cytotoxic activity against K562 cells [58]. Sotiropoulou and *al.*[8] finally showed that the co culture of Natural Killer cells in the presence of MSC altered that the cytotoxicity NK cells against HLA class I positive tumor cells, but not against HLA class I negative.

Again, the effect of the MSC depends both on cell contacts (inhibition of NK cells cytotoxicity) and of soluble factors synthesis (inhibition of proliferation and synthesis of cytokines by NK cells stimulated by IL-15). The secretion of PGE2 by the MSC is involved in the reduction of NK proliferation, of the CD56 antigen membrane expression and of the cytotoxicity, but does not intervene on the cytokines synthesis [8]. Blocking PGE2 or TGF- β helps to restore the NK cells proliferation capacity.

The MSC “immunological' privilege” that would protect them against NK cells lysis is also discussed. The MSC were first considered as cells that cannot be lysed by NK cells [54, 73]. Conflicting results have been reported, arguing that the MSC express various ligands recognized by activated NK cells [8, 74].

MSC and dendritic cells

The MSC immunomodulatory effect can also be explained by their ability to interfere with the differentiation, the maturation and the function of dendritic cells (DC). MSC can inhibit the monocyte-derived DC maturation by negative regulation of the CD11c and CD83 antigens expression, of the MHC Class II molecules and of costimulatory molecules. Similarly, a decrease in the production of pro-inflammatory cytokines (TNF-alpha, IFN-gamma and IL-12) and an increase in the anti-inflammatory IL-10 production were observed [9, 68, 75, 76]. It is therefore likely that the MSC inhibit the DC differentiation and lead to the emergence of immature DC. The suppressive effect of MSC on DC differentiation is partly related to the synthesis of soluble factors such as IL-6, M-CSF (macrophage colony-stimulating factor) or PGE2 [9, 68, 77, 78]. The inhibition of PGE2 synthesis restores TNF-alpha and IFN-gamma secretion by DC grown in the presence of MSC. Finally, Raghavan et al. showed that MSC were able to halt DC cell cycle at phase G0/G1 [79].

All these *in vitro* data demonstrate that MSC modulate the action of different cells involved in the immune response, and preferentially inhibit the T and B cells proliferation and the dendritic cells differentiation. The molecular mechanism of this immunosuppressive effect on dendritic cells and/or on T and B lymphocytes still remains poorly understood and sometimes contradictory. Indeed, the MSC immunosuppressive and immunomodulatory properties are based on a combination of many mechanisms, which also depend on the environment and

concern both the adaptive immunity and innate immunity. Divergent mechanisms of action could account for the diversity of their immunosuppressive effects and can be attributed to differences in the MSC origins, their isolation, their culture and their injection techniques.

2.4 Summary of relevant pre-clinical and clinical trials

2.4.1 MSC and experimental models of SLE

According to their in vitro immunomodulatory properties and their ability to induce tissue repair mechanisms, MSC have been proposed as a new therapy for several autoimmune diseases [80], in particular for scleroderma and lupus [81]. The large number of experimental data based on the administration of MSC from various sources in lupus murine models should be interpreted on the basis of cytokines and inflammatory environment and according to the type and timing of the MSC injections.

MRL/lpr, BXSB and NZB/W genetically prone lupus murine mice develop progressive nephritis, with high levels of serum autoimmune antibodies and immune abnormalities. Since the early 2000s, Kushida has shown that the concomitant injection of MSC enhances long-term survival after bone marrow transplantation in previously irradiated MLR/lpr mice [82]. In this context, the MSC improve HSC engraftment, but also the control of disease relapse [82]. In the BXSB SLE mouse model, Deng et al. showed that MSC injection was able to induce inhibition of self-reactive T and B cells [71]. In NZB/W and MRL/lpr SLE mice, treatment with allogeneic MSC allows to control clinical and biological markers of SLE disease and to restore a T regulatory Foxp3 + population [83]. The efficacy of MSC compared to conventional cyclophosphamide (CY) has been studied in MRL/lpr mice [83, 84]. MSC injection allowed a significant reduction of double stranded (dsDNA) anti-DNA antibody levels, anti-nuclear antibodies (ANA), serum immunoglobulin IgG1, IgG2a, IgG2b and IgM and an increase in serum albumin. Conventional CY treatment decreased the levels of serum autoantibodies and of IgG2a immunoglobulins, increased the albumin levels to a lesser extent compared to MSC, and did not decrease the immunoglobulins IgM, IgG1 and IgG2b levels. In this model, MSC injection reduced the proteinuria and IgG and C3 complement glomerular deposition and restored the glomerular structure. Although CY allowed to reduce IgG glomerular deposits, it did not restore the glomerular structure nor reduced the C3 accumulation [83, 84]. MSC transplantation allows to prolong the mice survival. These effects are associated with a decrease in Th1 (IFN-γ, IL-2) and in pro-inflammatory (TNF-α, IL-6, IL-12) cytokines and an increase in Th2 (IL-4, IL-10) cytokines. In vitro co-culture shows that the MSC inhibit the lymphocyte proliferation and splenocytes only, but not the mesangial proliferation [85, 86]. In their study, Ma and al. showed that MSC injection in MRL/lpr mice improves nephritis via the removal of the excessive B cells activation through inhibition of BAFF production [87].

L. Sun and colleagues showed that MSC isolated from Umbilical Cords administered in MRL/lpr mice reduce lupus nephritis in a dose-dependent manner [84, 85]. The MSC injection resulted in a reduction of 24 hours proteinuria, serum creatinine, anti-dsDNA antibodies and the extent of kidney damage. These effects are associated with inhibition of the renal expression of MCP-1 and HMGB-1 as well as with an increase in Foxp3+ regulatory T-cells. In the NZB/W F1mouse, Chang et al. showed that injection of Umbilical Cords derived MSC significantly delays the onset of proteinuria, reduced the anti-dsDNA antibodies levels and the renal lesions, and prolonged survival. These effects were related to the inhibition of T lymphocytes proliferation, the induction of Th2 cytokines production and the inhibition of pro-inflammatory cytokines production [86]. Recently, Chen J. et al showed that activated autophagy increased apoptosis of T cells in SLE patients, and UC-MSCs could inhibit respiratory mitochondrial biogenesis in activated T cells to downregulate autophagy and

consequently decrease T cell apoptosis through mitochondrial transfer [88]. The aberrant generation or activation of T follicular helper (Tfh) cells contributes to the pathogenesis of SLE.In their study, Zhang et al.reported that UC-MSCs could effectively inhibit Tfh cell expansion through the activation of iNOS in lupus-prone B6-lpr mice, which are highly dependent on cell-to-cell contacts [89].

2.4.2 MSC clinical use in humans

Properties of the MSC obtained from autoimmune diseases (AD) patients

In vitro data obtained from bone marrow derived MSC from autoimmune diseases (AD) patients are heterogeneous. Early results showed that bone marrow derived MSC from patients with Rheumatoid Arthritis, Scleroderma, Sjögren syndrome or SLE showed some antiproliferative properties against activated T cells, but conflicting results were observed in terms of proliferation and differentiation.

In a study of 7 SLE subjects, Papadaki and *al.* [90] showed a reduced number of bone marrow HSC compared with healthy subjects and a significant decrease in hematopoiesis support by the MSC, which could be attributed to an intrinsic MSC deficit or immune dysregulation. Indeed, bone marrow derived MSC from SLE patients show decreased proliferation compared to healthy donors and a specific morphology of senescence [91, 92]. Such senescence is associated with abnormalities in gene expression accounting for abnormalities in the actin cytoskeleton and in the cell cycle regulation involving BMP/TGF-β and MAPK signaling pathways. In their study, Gu et al.[93] found that the senescence of the SLE patients derived MSC was associated with an inability to increase regulatory T cells. An increase in the p16Ink4a expression plays a major role in this cell senescence process via regulation of cytokine secretion and ERK1/2 signaling pathway. The Wnt/β-catenin signaling via the p53/p21 pathway also plays an essential role in the senescence of MSC from SLE patients. Finally, the MSC from SLE patients show increased apoptosis, with a decrease in Bcl-2 and an increase of cytochrome C, as well as an overproduction of intracellular ROS with p-FOXO3 and AKT upregulation [93].

Preclinical data on the characteristics of the autologous MSC from AD patients as well as the reassuring safety data regarding the use of MSC from healthy allogeneic donor underlined the importance of using allogeneic MSC from healthy donors for clinical application to AD patients [94].

Use of MSC as immunosuppressive therapy in humans

MSC first injections in the treatment of hematological or oncological diseases

The first clinical trial using MSC was performed in 15 subjects with hematological malignancy receiving intravenously injected autologous MSC. No immediate or late side effects have been observed [95]. The second trial involved 28 breast cancer subjects who received autologous peripheral blood hematopoietic stem cells after high dose chemotherapy. Autologous MSC were injected before the HSC. The duration of aplasia was shorter than 8 days to reach higher than 500/mm^3 neutrophils, and 8.5 days to reach over 20,000/mm^3 platelets [96]. No immediate or late side effects were observed after the MSC injection. Given the difficulties to obtain a sufficient number of autologous MSC (altered stroma with previous chemotherapy), autologous MSC were then replaced by allogeneic bone marrow MSC derived from a healthy donor.

In 2005, Lazarus et *al* presented results of a trial assessing the contribution of allogeneic MSC (with increasing doses of 1, 2.5 and 5 x 10^6/kg) to allogeneic geno-identical HSC graft (MSC and HSC from the same donor) [97]. Forty-six subjects with hematological malignancy received an MSC injection before HSC transplantation. The probability of survival without disease or progression at 2 years was 53%. Compared to a group of historical controls, the test showed no acceleration of the hematopoietic reconstitution or prevention of Graft-Versus-Host reaction.

In the treatment of GVHD refractory to conventional therapy, K Leblanc et al. results raised high expectancies when injection of haplo-identical MSC derived from the mother of the young patient allowed effective control of acute hepatic and digestive GVHD refractory to all lines of immunosuppressive drugs [10]. No immunization against the haplo-identical MSC appeared. Other studies involving a higher number of subjects have confirmed the hypothesis that the MSC represent an alternative treatment for acute severe GVHD patient in the post-HSC transplant setting [98]. In 55 patients treated by MSC injection for acute severe GVHD cortico-resistant after HSC transplant [99], Leblanc et *al* reported a complete response in 30 patients and partial response in 9 others. Preliminary results from use of MSC to control GVH illustrate the capacity of MSC to inhibit, or at least to modulate the immune response after allogeneic HSC transplantation. Further developments are ongoing with the use of allogeneic bone marrow MSC derived from healthy donors in the European randomized trial vs placebo (Hovron, Horizon 2020, Coordinator Pr W Fibbe).

Use of the MSC in the context of Autoimmune Diseases

In July 2016, ClinicalTrials.gov database records in Europe, China and US 131 trials using injection of autologous (62) or allogeneic (69) MSC: 5 trials in lupus, 31 in the multiple sclerosis, 16 in diabetes type I, 6 in rheumatoid arthritis, 11 in Crohn's disease, 2 in systemic sclerosis (including one coordinated by our team to the title of the PHRC AOM11250) and 1 in Sjögren's syndrome. Despite the ongoing phase I/II clinical trials in AD subjects and sustained reassuring data concerning the safety of MSC clinical use in the early clinical studies, few results are still published in the field of autoimmune disease [100]. There is a lack of standardization of cellular products. The MSC sources vary according to each trial: bone marrow, adipose tissue, placenta and umbilical cord and the MSC can be either autologous or allogeneic. Data from the literature are sometimes conflicting according to studies when using autologous MSC and for these reasons, it is best to consider the use of allogeneic MSC to treat AD patients. Several clinical cases have been published using allogeneic MSC for multiple sclerosis patients [101]. A German team treated 5 Systemic Scleroderma patients with allogeneic bone marrow derived MSC [102] with no major adverse effects or specific anomalies reported after a respective follow-up of 44 months, 24 months, 6 months, 23 months and 18 months. Our team is currently coordinating a trial of phase I - II funded by the PHRC 2011 (AOM 11250) to analyze the feasibility and the tolerance of the administration of MSC from Bone Marrow derived allogeneic healthy donors in the treatment of 20 patients with severe or rapidly progressive or refractory to prior therapies systemic sclerosis. So far 6 patients were injected without any observed toxicity.

Use of MSC for the treatment of SLE

Lupus is frequently observed in China and therefore major clinical trials concerning the use of allogeneic MSC for SLE patients were conducted by the Chinese teams [103]. 87 SLE patients refractory to conventional therapy were reported so far after treatment by injection of allogeneic bone marrow or umbilical cords derived MSC [83, 85, 86, 104, 105].

Data of safety and efficacy on these patients show similar results to those obtained after autologous peripheral HSC transplantation for severe SLE with respectively 28%, 31%, 42% and 50% of complete response as assessed on SELENA-SLEDAI at 1, 2, 3 and 4 years post injection [86, 106, 107] In a multi-center clinical trial in China on 40 active severe SLE patients refractory to standard therapy using cyclophosphamide or MMF with cortico-dependency and with SLEDAI score > 8 or at least one visceral grade A or 2 visceral grade B according to the BILAG score, 32% of the patients were in major clinical response (MCR 13/40) and 27% in partial clinical response (PCR 11/40) during the 12 months of follow-up after MSC injection. However, 7 out of 40 (17.5%) patients have a disease recurrence within six months of follow-up, after prior clinical response, suggesting the potential benefit from repeated MSC treatment after 6 months [106]. MSC therapy induces remission of lupus nephritis, SLE diffuse alveolar hemorrhage [104, 108]and refractory cytopenia [104].

The long-term safety of allogeneic UC-MSCs transplantation for 9 patients with refractory SLE was reported by Wang D. et al [109]. There was no change in peripheral white blood cell count, red blood cell count and platelet number in these patients after followed up for 6 years. Liver functional analysis showed that serum alanine aminotransferase, glutamic-oxalacetic transaminase, total bilirubin and direct bilirubin remained in normal range after MSCs infusions. No newly onset abnormality was detected on electrocardiogram and chest radiography. Moreover, they found no rise of serum tumor markers, including AFP, CEA, CA125 and CA199, before and 6 years after MSCs infusions.

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

A total of 10 patients will be included over 42 months. The number of patients is not necessary to be justified when using a Bayesian test analysis in a phase I – II trial

2.6 Name and description of the investigational medicinal product(s)

In this Research, the investigational medicinal product or drug product is called Human umbilical cord tissue (hUCT) derived allogeneic MSCs for treatment of refractory Systemic Lupus Erythematosus (SLE) (UC-MSC) (drug product).

The drug substance will be produced by the Centre for Cell Gene & Tissue Therapeutics (CCGTT) at the Royal Free Hospital (Prof. Mark Lowdell). Cord tissue was manually dissected, before enzymatic then mechanical dissociation to isolate MSCs. MSC selection occurs through plastic adherence, then cells are expanded in 2D culture. The drug substance is manufactured from a Primary Seed Stock (PSS) from which Working Cell Stocks (WCS) are obtained. The PSS consists of cryopreserved passage 1 (P1) MSCs in cryovials of approximately $1x10^6$cells per ml; the WCS consist of cryopreserved passage 2 (P2) MSCs in bags of up to $5x10^6$ per ml.The WCS, cryopreserved in bags, will be shipped to Saint-Louis Hospital Cell Therapy Unit (Pr J.Larghero). Then, one bag per patient will be thaw to seed multi-layer CellStacks, and cultured for 4 days to obtain the final medicinal product (passage 3) to be grafted to patient.

Cord donor meets the following criteria:
- Healthy volunteer; Complies with European directive 2006/17/EC concerning the technical requirements for the donation, obtaining and control of tissues and cells of human origin;
- Mother informed consent signed.

UC-MSCs characterization was established according to the recommendations of the EMEA/CHMP/410869/2006 (Guideline on Human Cell - Based Medicinal Products). The characterization is based on:
- The identity and purity: immunophenotype;
- Safety: microbiological sterility, endotoxins and mycoplasma research;
- Genetic stability: karyotype;
- The potential: a) proliferative capacities evaluated by CFU-F; b) quantification of the immunosuppressive activity on the activation and proliferation of T (Mixed lymphocyte response assay). Data will be gathered throughout the trial to determine the suitability of these assays for prediction of potency.

The manufacturing process is compliant with GMP requirements. After UC-MSC harvest and quality control, the final product (suspension of allogeneic UC-MSC in saline solution and albumin, containing the exact dose of UC-MSC for the patient) will be released.

Table 1 The specifications for the release criteria of the cell therapy medicinal product are**:**

Description	**Method**	**Release criteria**
Cell count	Haemacytometer	= cell dose/kg patient
Viability	Flow cytometer	≥ 80%
Immunophenotype	Flow cytometer	CD90+ ≥ 90% CD73+ ≥ 90% CD105+ ≥ 80% CD45+ ≤ 2%
Sterility *	Automated CO_2 detection	Absence of germs

*Results will be obtained 10-day after administration to the patient. In case of positive results occurring, the identity of bacterial strain and antibiogram will be transmitted to the clinician in order to implement an adapted antibiotic treatment.

There is a process for exceptional release in the event that release specifications are not met (under conditions which do not exceed 10% of the specifications). Release of non-conforming products is performed with notification and accordance of physician.

Additional informations will be obtained after the release for the characterization of the product: karyotype, CFU-F, and mixed lymphocyte response assays (non-release criteria).

After release, the medicinal product will be shipped to the clinical unit and administered by slow intravenous infusion. Non-serious adverse events in relation to a potential reaction during or after the injection of the UC-MSC may occur. These side effects will be supported by adequate drugs if necessary (antihistamines...) and the infusion rate will be decreased. These side effects will be notified on the tracability of MSC injection sheet.

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

Initially 5 subjects at the initial dose of 2.10^6 Allogeneic Umbilical Cord derived-MSCs/kg recipient weight will be included.
Then, an intermediate analysis after the inclusion of 5th patient and within 3 months of inclusion by DBIM at Saint Louis Hospital and DSMB will permit to validate if the following 5 subjects will be enrolled in a dose:
- 1.10^6 MS /kg there is a high probability of excessive toxicity (according to observed toxicity) at 2.10^6 MSC / kg;
- 4.10^6 CSM/kg if there is a low probability of excessive toxicity at 2.10^6 CSM / kg

The Allogeneic UC-MSC will be injected to the patient by slow intravenous infusion according to the weight of the recipient and patient groups in the study, at doses of:
- 1.10^6 CSM / kg
- 2.10^6 CSM / kg
- 4.10^6 CSM / kg

1 injection during 30min to 1h by Intravenous infusion

See Appendix 3 "NOTICE D'INJECTION DU PRODUIT EXPERIMENTAL" (Essai clinique MSC-SLE)" for further information about the administration of the product.

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

Benefits:

The injection of MSCs must allow to have an immunomodulatory and immunosuppressive action and to slow down the progression of the disease while trying to regress the intensity of the fibrosis, in particular renal. These immunosuppressive, immunomodulatory and anti-fibrosing properties of MSC have been demonstrated by our team in Systemic Sclerosis and by many authors both in the laboratory, in animals and have also been used in humans especially in China (Pr Sun) and in the USA (Pr Gikelson). The first injections of CSM with very promising results were carried out in 2001 and published in 2005 for the treatment of chronic marrow transplant rejection. Since then, MSCs from umbilical cords have been injected into humans for the treatment of many autoimmune diseases, including lupus. The results reported during lupus show an improvement in the signs of activity of lupus disease with improvement of renal function, joint damage and proteinuria regression in a significant way in more than 400 patients in England, United States and China and in the USA.

Risks : Concerning the risks associated with the examinations, they are described in the table below:

Table 2 : Risks associated with the examinations

Patient's exams	Risks related to examinations
Patient Information and Signature of Consent	None
Medical History and History of Autoimmune Disease	None

Detailed physical examination (skin, heart, lung, skeletal muscles and joints)	None
Detailed clinical examination (weight, height, concomitant treatment)	None
Biological examinations (hematology and biochemistry, 24h proteinuria, ECBU, serology (HIV 1/2, HTLV 1/2, Hepatitis B and C) and optional viral load (HIV 1/2, Hepatitis B and C)	Very mild risks associated with blood sampling and urine harvesting for ECBU and 24h proteinuria (urinary tract)
Dosage of β-HCG	Very mild risks associated with blood sampling
Blood gas	Very mild risks associated with blood sampling
Chest X-ray and ECG	X-rays are safe because of the very low doses used. Risks related to pregnancy, report it.
Cardiac ultrasound and if necessary: MRI or CT scan	Cardiac ultrasound: none: Ultrasound, as part of their use in ultrasound, have never revealed any harmful consequences in humans MRI: Risks related to the magnet: avoid any metal object on or in the body, risks related to pregnancy, report it. The risks associated with the injection of a contrast agent: possible allergic reactions, these complications occur mainly within the quarter of an hour following the injection of the contrast medium. Therefore, it is important to take a few minutes rest in the cabin or in the waiting room. CT Scan: The doses used are low during the examination and therefore do not cause undesirable effects on the health. Risks related to pregnancy, report it
Consultation of stomatology (teeth, gums ...)	None
Specific routine immunological examinations: immune profile (autoantibodies, C3, C4 and CH50 complement proteins)	Very mild risks associated with blood sampling
Routine Immuno-phenotyping of lymphocytes	Very mild risks associated with blood sampling
Cytokines Dosage	Very mild risks associated with blood sampling
Daily dose of corticosteroids	The risk of these adverse effects varies according to the doses received and the duration of the treatment. Some adverse effects occur mainly during prolonged treatment (eg adrenal insufficiency, hypercholesterolemia), while others may occur from the very first days of treatment (eg insomnia, increased appetite). Most adverse effects induced by corticosteroids are not serious and disappear when treatment is decreased or stopped
Cellulotheque / DNAtheque	Very mild risks associated with blood sampling
Sérothèque / Plasmathèque	Very mild risks associated with blood sampling

At present, there have been no serious adverse reactions expected in the human use of MSCs. Some transient, benign adverse effects associated with the injection procedure (risk of intervention) or biopsy are likely to occur, such as pain and / or redness at the point of puncture, respiratory discomfort, chest pain, Erythema, headache, dyspnea, rash, chills / hyperthermia, changes: RT / pulse ...

3 OBJECTIVES

3.1 Primary objective

To assess the early tolerance of allogeneic UC derived MSC administration for severe SLE refractory to standard therapies (cyclophosphamide (CY), mycophenolate mofetil (MMF) and corticosteroids with or without prior anti-CD20 therapy) at ten days.

3.2 Secondary objectives

1 Feasibility of allogeneic UC-MSC administration in the treatment of severe SLE subjects refractory to conventional therapies
2 Tolerance three months after injection, considering the observed morbidity and the overall survival in SLE treated subjects until 1 year after the procedure.
3 Analysis of biological and clinical response on routine clinical and biological examination and criteria for lupus monitoring using: SELENA-SLEDAI, BILAG, Indices of quality of life (SF36, EQ5D), Systemic Lupus Erythematosus Responders Index (SRI): evaluation of the comorbidity by the damage index SLICC-SLE scores and the daily dose of corticosteroid, and Charlson Comorbidity Index.
4 Analysis of the efficacy at 3-months after injection of allogeneic UC-MSCs according to the proportion of patients with Major Clinical Response (MCR).
5 Percentage of patients with Partial Clinical Response (PCR) during the 12 months of follow-up study.
6 Evaluation of the immunomodulatory effect on :
   - Standard Immunological and biological markers, including lymphocytes immuno-phenotyping: complete blood count, creatinine, proteinuria 24h, autoantibodies (anti-DNA antibodies and native ANAs), complement system C3, C4 and CH50,immunophenotyping at M0, M1 and every three months during the follow-up period of the study (M3, M6, M9 and M12).
   - Analysis of specific cytokine production at M0, M1 and M3 by K Tarte SITI Laboratory (CHU Rennes).
7 Analysis of MSC immunogenicity at M0, M1 and M3

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

Immediate tolerance will be assessed during the injection and within the first 10 days following the MSC injection, according to side effects defined by CTCAE standards (Miller Results of cancer treatment Cancer 1981; 47 (1): 207 - 214). Treatment-related toxicity will be analyzed according to the international World Health Organization (WHO) (maximum degree of toxic attacks by the body). ***An injection will be considered as not tolerated for any toxicity criteria above grade ≥ 3*** (Tugwell P et al, Omeract OMERACT trials 2007)***.***

This ten-day primary endpoint was chosen in an analogy with another phase I / II cell therapy trial currently underway (PHRC AOM 11 250) and analyzing "the tolerance of allogeneic MSC administration in the treatment of SSc diffuses severe or rapidly progressive and refractory to the conventional treatments by cyclophosphamide previous "for which the prior authorization of the ANSM was obtained on this same criterion. It seemed important to homogenize the practices, the criteria of judgment and ultimately the analyzes. Moreover, following this remark,

we decided to explicitly continue the analysis of tolerance by adding secondary endpoints of tolerance during the course of M1, M3, M6 and M12.

4.1.2 Secondary endpoints

Safety Tolerance will be assessed~~,~~ at M1, M3, M6 and M12 according to side effects defined by CTCAE standards (Miller Results of cancer treatment Cancer 1981; 47 (1): 207 - 214). Treatment-related toxicity will be analyzed according to the international World Health Organization (WHO) (maximum degree of toxic attacks by the body). ***An injection will be considered as not tolerated for any toxicity criteria above grade ≥ 3.***

Proportion of patients with Major Clinical Response (MCR) and the proportion of patients with Partial Response Clinic (PCR) during the 12 months of study follow-up at 3, 6, 9 and 12 months (M3, M6, M9 and M12).

After the MSC injection (M0), the doses of corticosteroids and immunosuppressive therapies will be reduced according to the patient clinical status improvement following clinical evaluation at M1 M3 M6 M9 and M12.

For responder patients, the dose of prednisone will be reduced by 5mg every 2 weeks during the months after the MSC administration

Responders are defined according to the evaluation at M1 after injection by a BILAG score between C and E and having no more than one organ with a BILAG B score and without having a new BILAG A or B score.

Non -responders are defined according to the evaluation at M1 after injection if the clinical index or the disease activity indices do not regress, ongoing treatments will not be reduced and other treatments can be introduced.

A flare will be defined as at least one new domain with BILAG A score or two new domains with BILAG B scores from MSC infusion.

A MCR is defined as achieving BILAG C scores or better in all organs at 6 months without experiencing a severe flare and maintenance of this response throughout the 12-month study period.

A PCR is defined as (1) BILAG C scores or better and maintenance of this response without a new BILAG A or B score within 3 months; and (2) having no more than one organ with a BILAG B score at 6 months without achieving at least one new BILAG A or B score throughout the 12-month study period.

Clinical relapse will be defined as development of at least one new domain with a BILAG A or B score after a previous MCR or PCR.

No clinical response will be defined as failure to meet the definition of a MCR or PCR.

2- Disease activity measured by the BILAG scores (0 and 72) and SELENA-SLEDAI (0 to 105) every 3 months, as compared to inclusion, until the end of the follow-up period (M0, M1, M3, M6, M9 and M12).

3- SRI response rate, measured every three months (M3, M6, M9 and M12) during follow-up: a SRI response is defined as a 4 points reduction of SELENA SLEDAI-score, no new BILAG A score for an organ and no more than one new BILAG B score and no worsening (increase of 0.3) in the overall evaluation of the physician as compared to inclusion values.

4- Quality of life assessed by the Short Form 36 version 2 (SF-36v2) and the EQ5D before injection and every 3 months until the end of the monitoring period (M0, M3, M6, M9 and M12) and at M1.

5. Percentage of subjects with an average dose of prednisone reduced by 25% compared to M0 and who will be <7.5 mg / day for weeks 40 to 52. The average daily corticosteroid dose will be measured every 3 months until the end of the monitoring period (MO, M3, M6, M9 and M12).

6- The number of treatment failure defined by one of the following:
- end stage renal disease requiring dialysis or transplantation
- sustained doubled creatinine value from the two lowest values observed between screening and baseline and confirmed four weeks later.
- active lupus nephritis attributed to active SLE as defined by either of the two criteria:
  i. a doubling value of proteinuria: proteinuria> 1 g / 24 hours for the subjects who were <0.5 g / 24 hours at baseline or proteinuria> 2 g / 24 hours for the subjects who were> 1g / 24 hours at baseline
  ii. nephropathy with a 25% increase in serum creatinine with respect to the value at baseline and simultaneously having a value of proteinuria doubled up at least 2 g / 24 hours, hematuria (two positive urine test strips) and the presence Cell cylinders.

  These two criteria must be confirmed twice at 2-week intervals.
- need for steroid therapy intravenously, plasmapheresis, immunoglobulin IV or other immunosuppressive therapy to treat aggravation of SLE.

7. Presence of comorbidities according SCLICC-SLE index at M0 and every three months during study follow-up (M3, M6, M9 and M12) and Charlson Comorbidity Index at eligibility.

8- Standard Immunological and biological markers at M0, M1, M3, M6, M9 and M12: complete blood count, creatinine, proteinuria 24h, complement system C3, C4 and CH50 at M0 but not at M9.

9- Immune Profile with a detailed analysis of :
- lymphocytes immunophenotyping at M0, M1, M3, M6 and M12 (K Tarte SITI laboratory in Rennes)
- cytokines at M0, M1, M3 (K Tarte SITI laboratory in Rennes)
- and autoantibodies at M0, M1, M3, M6 and M12 (Laboratory of Immunology, Hospital St-Louis, Paris).

10) Analysis of MSC **immunogenicity** at M0, M1 and M3, according to:
- anti-HLA antibodies dosage
- cross-match analysis

4.2 Research methodology

4.2.1 Design of the trial

Clinical study (phase I-II), non-comparative, not randomised, not controlled, no blinding (open label).

4.2.2 Number of participating sites

Single center phase I-II open study with national recruitment within the FAI2R network.
The subjects will be recruited: in hospital (out-patients or in-patients).

4.2.3 Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) (here: 001) - Sequential selection number for the site (4 digits) (here: 100X) - surname initial (here: the first letter) - first name initial (here: the first letter)
This reference number is unique and will be used for the entire duration of the trial.

Table 4: Summary table of the specialist doctor and type of visit for each visit reported in this protocol

Visit	**The specialist field of the doctor**	**Type of Visit**	**Time frame for each visit**
Eligibility(1)	Internal Medicine, Biologists, Radiolog	at the hospital	4 months before M0 +/- 1 week

M0 =MSC injection	Internal Medicine, Biologists and Radiolog, Researchers	at the hospital	Baseline visit
D10	Internal Medicine and Researchers	calling appointment	10 days after M0
M1	Internal Medicine, Biologists and Researchers	at the hospital	1 month after M0 +/- 1 week
M3	Internal Medicine, Biologists and Researchers	at the hospital	3 months after M0 +/- 1 week
M6	Internal Medicine, Biologists and Radiolog, Researchers	at the hospital	6 months after M0 +/- 1 week
M9	Internal Medicine and Biologists	at the hospital	9 months after M0 +/- 1 week
M12	Internal Medicine, Biologists and Radiolog, Researchers	at the hospital	12 months after M0 +/- 1 week

5.1 Screening visit (Eligibility visit)

The screening visit takes place between Months-4 (M-4) and 1 days before the baseline visit.

The following assessment will be scheduled before the inclusion of the patient in the study, and therefore before the beginning of the treatment:

- Medical history and history of autoimmune disease and treatments,
- Detailed physical examination, particularly of the skin, heart, lungs, Skeletal muscles and joints
- Detailed clinical examination including date of birth, gender, weight, size, concomitant therapy
- SLE activity Scores: BILAG and SELENA-SLEDAI, SRI
- SLE Damage Index : the SLE SLICC/ACR
- Quality of life SF-36 questionnaire, EQ5D
- Biological examinations including:
  - **Hematology:** Sedimentation rate, hemoglobin, hematocrit and WBCs with leukocyte, and platelets counts
  - **Biochemistry:** serum electrolytes and creatinine clearance, renal and liver function, serum protein electrophoresis, 24h proteinuria, urinary cyto-bacteriological analysis, ECBU.
- Daily Dose of Corticosteroïds
- Pulmonary chest X ray
- EKG
- Echocardiography (pericardial effusion and AHT) and if necessary MRI cardiac or chest CT scan with measurement of LVEF
- Blood gases (pO2, pCO2, p(A-a) O2) [59] directed at room temperature only if there is a suspicion of pulmonary.
- Somatology consultation with evaluation of the teeth and gums
- Pregnancy test (β-HCG dosage)
- Validation of eligibility : respect for the Inclusion Criteria (IC) and the Non Inclusion Criteria (NIC)

To evaluate MSC immunogenicity, detection and identification of anti-HLA antibodies from donor (single umbilical cord) will be realized in patients before and after administration of MSC.

Table 5: Summary table of Whose, Who and When individual's consent is collected

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
• the subject participating in the trial; • an appointed representative;	• the Principal investigator (specialist in Internal Medicine) • the co-investigator designed	• Screening visit (Eligibility visit)	• After 24h of reflection of the patient and that Eligibility criteria have been approved by Principal Investigator....

5.2 Baseline visit

For Baseline visit, the verification of inclusion and exclusion criteria will be performed at M0.
The following assessments will be performed at M0:

- Detailed physical examination, particularly of the skin, heart, lungs, Skeletal muscles and joints
- Detailed clinical examination including date of birth, gender, weight, size, concomitant therapy
- Evaluation of tolerance according to the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02
- SLE activity Scores: BILAG and SELENA-SLEDAI, SRI
- SLE Damage Index : the SLE SLICC/ACR
- Quality of life SF-36 questionnaire, EQ5D
- Biological examinations including:
  - **Hematology:** Sedimentation rate, hemoglobin, hematocrit and WBCs with leukocyte, and platelets counts
  - **Biochemistry:** serum electrolytes and creatinine clearance, renal and liver function, serum protein electrophoresis, 24 h proteinuria, urinary cyto-bacteriological analysis, ECBU.
- Immunology on 24ml gel-free lithium heparin tubes + 14ml dry tube :
  - Cytokines Phenotypic analysis of T Lymphocytes / LB Lymphocytes / NK / monocytes / Dendritic Cells
  - Lymphocyte subpopulations of T, B and NK cells, conducted by FACS analysis,including :
    - CD4 Treg cells,identified by a double marking of CD25 and CD127 [110]
    - NK cells, characterized by a double marking CD16 and CD56. CD19+ and CD5+ B cells involved in autoimmunity, will be also characterized.

    The following associations will be used with ad ho cell surface markers:
    - CD45 / CD3 / CD4/ CD8/CD16-56/CD19
    - CD45/CD14/CD16 / CD56 / CD3
    - CD45/CD5 / CD19 / CD10/CD38/CD27/IgD
    - CD45/CD127 / CD3 / CD4 / CD25 / CD31 / CD45RA
  - MSC immunogenicity:
    - Detection and identification of anti-HLA antibodies
    - Crossmatch analysis
- Determination of anti DNA autoantibodies by ELISA on a 7 ml dry tube:
  - anti-DNA antibody (IgG, IgM)
  - Soluble nuclear antigen antibody (anti SSA, SSB, anti-Sm, anti RNP)
  - Anti-nuclear antibodies (IgG)
  - Anti-cardiolipin (IgG, IgM) antibody
  - Antibody anti-Beta2 glycoprotein 1 (IgG, IgM)
- C3, C4, CH50 complement factors levels
- Daily Dose of Corticosteroïds
- Pulmonary chest X ray
- EKG

The injection of CSM takes about 30min to 1h under the supervision of a Study Nurse and the Principal Investigator who analyses the patient' tolerance during the injection of MSC administration and therefater at one hour, and during the 24 hours after injection of the MSCs.

Clinical data are reported at 0, 5, 10, 15, 30, 45, 60, 90 min (arterial pressure, frequency, T°C, Sat O2, Remarks) after MSC injection and clinical observation during 24 hours is performed including among other things:
- Reportable Incident
- Incident during injected
- Delayed Incident
- Hypotension / hypertension
- Thrill / hyperthermia
- Local inflammation
- Tachycardia / bradycardia
- Nausea / Vomiting
- Other Symptoms

5.3 Follow-up visits

The following assessments will be performed at **D10 after** mesenchymal stem cells injection

- Detailed clinical examination, including weight, size, and concomitant treatment.
- Detailed physical examination, particularly of the skin, heart, lungs, muscles and joints
- Evaluation of tolerance according to the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02
- Patient survival

The following evaluations will be realized at M1, M3, M6, M9 and M 12 after MSC injection:

- Detailed clinical examination, including weight, size, and concomitant treatment.
- Detailed physical examination, particularly of the skin, heart, lungs, muscles and joints
- Evaluation of tolerance according to the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02
- SLE activity Scores:, BILAG and SELENA-SLEDAI, SRI
- SLE Damage Index : the SLE SLICC/ACR
- Quality of life SF-36 questionnaire, EQ5D
- Biological examinations including:
    - **Hematology:** Sedimentation rate, hemoglobin, hematocrit and WBCs with leukocyte, and platelets counts
    - **Biochemistry:** serum electrolytes and creatinine clearance, renal and liver function, serum protein electrophoresis, 24 h proteinuria, urinary cyto-bacteriological analysis.
- Immunology on 24ml gel-free lithium heparin tubes + 14ml dry tube:
    - Cytokines (but not at M6, M9 and M12) Phenotypic analysis of T Lymphocytes / LB Lymphocytes / NK / monocytes / Dendritic Cells (but not at M9)
    - Lymphocyte subpopulations of T, B and NK cells (but not at M6, M9 and M12), conducted by FACS analysis, including:
        - CD4 Treg cells,identified by a double marking of CD25 and CD127 [110]
        - NK cells, characterized by a double marking CD16 and CD56. CD19+ and CD5+ B cells involved in Autoimmunity, will be also characterized.

      The following associations will be used with ad ho cell surface markers:

- CD45 / CD3 / CD4/ CD8/CD16-56/CD19
- CD45/CD14/CD16 / CD56 / CD3
- CD45/CD5 / CD19 / CD10/CD38/CD27/IgD
- CD45/CD127 / CD3 / CD4 / CD25 / CD31 / CD45RA

- MSC immunogenicity (but not at M6, M9 and M12):
  - Detection and identification of anti-HLA antibodies
  - Crossmatch analysis

- Determination of anti DNA autoantibodies by ELISA on a 7 ml dry tube (but not at M9):
  - anti-DNA antibody (IgG, IgM)
  - Soluble anti-nuclear antigen antibody (anti SSA, SSB, anti-Sm, anti RNP)
  - Anti-nuclear antibodies (IgG)
  - Anti-cardiolipin (IgG, IgM) antibody
  - Antibody anti-Beta2 glycoprotein 1 (IgG, IgM)
- C3, C4, CH50 complement factors levels (but not at M9)
- Daily Dose of Corticosteroïds
- Pulmonary chest X ray (but not at M1)
- Blood gases (pO2, pCO2, p(A-a) O2) [59] directed at room temperature only if there is a suspicion of pulmonary (but not at M1, M3, M6 and M9).
- EKG (but Not at M1, M3 and M9)
- Pregnancy test (β-HCG dosage) (but not at M1, M3, M6 and M9)

5.4 End of study visit

The End of the study is when all inclusions and all patients finished all their follow-up.
The last visit of this study is visit M12.
The methods of taking care of the persons included in this research are the same as those envisaged in the framework of their usual management of their disease, within the framework of the current care.

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

The total duration of the study is 54 months with a period of patient's inclusion of 42 months. Duration of patient's participation will be 1 year. Patients will be included and followed in the Internal Medicine Auto-Immunes Diseases and Vascular Pathology Unit (UH 04) and allogeneic UC derived MSC preparations will take place:

a) In the UCL cell laboratory
b) And then delivered by the laboratory of Cellular therapy at Saint Louis hospital (see table 6 below):

Table 6: Summary table of Clinical Centers, Laboratories and Associate Clinical Investigator implies in this protocol

Clinical centers responsible for the recruitment and monitoring of patient	Responsible for Cellular therapy laboratories of cell production
St-Louis Hospital, AP - HP, Internal Medicine: Auto-Immunes Diseases and Vascular Pathology Unit, UH 04, 1 avenue Claude Vellefaux, 75010 Paris. **Investigator Coordinator:** Pr Dominique FARGE-BANCEL	Cell therapy Lab, UCL **Manager:** Pr Mark Lowdell Cell Therapy Unit, St-Louis Hospital, AP - HP, 1 avenue Claude Vellefaux, 75010 Paris **Manager:** Pr Jérôme Larghero **Co-leader:** Dr. Audrey Cras

Clinical Centers which only address patients to Pr Farge	Associate Clinical Investigator which only address patients to Pr Farge
Reference Center for Lupus **Civil Hospital***, Internal Medicine service, 1 place of the hospital, 67091 Strasbourg.	Pr Thierry MARTIN*
PURPAN Hospital*, University Hospital of Toulouse, Internal Medicine service, Place du Dr Joseph Baylac, 31300 Toulouse	Dr Grégory PUGNET*
National Reference Center of Rares and Systemic Auto-Immunes Diseases, Lupus and antiphospholipid antibody syndrome, Vasculitis, Myositis, Gougerot Sjögren, Polychondritis, Immunological thrombocytopaemia, Sarcoidosis, Sharp, Still, Clarkson* **E3M Institut La Pitié Salpêtrière-Charles Foix - Pitié-Salpêtrière Hospital** 47-83 boulevard de l'Hôpital	Pr Zahir AMOURA*

**with the participation of « Filière des Maladies Auto-Immues et Auto-Inflammatoires Rares (FAI2R) »*

Table 7: Summary table of total study duration

• Maximum period between screening and enrolment	4 months
• Length of Inclusion period	42 months
• Duration of participation for each subject, of which:	
◦ Treatment period:	1 injection of UC-MSC of 30min to 1h
◦ Follow-up period:	12 months
Total study duration:	54 months

5.6 Table 8: Synopsis table of exams to achieve during the study summarising the chronology of the study

Patient examination	Eligibility[(1)]	M0 =MSC injection	D 10	M1	M3	M6	M9	M12
Patient Information and signature of informed consent	X							
Medical history and autoimmune disease history	X							
Detailed physical examination (skin, heart, lungs, skeletal muscles and joints)	X	X	X	X	X	X	X	X
Detailed clinical examination (date of birth, gender, weight, size, concomitant therapy)	X	X	X	X	X	X	X	X
SLE SLICC/ACR	X	X		X	X	X	X	X
Charlson Comorbidity Index	**X**							
SELENA-SLEDAI, BILAG, SRI	X	X		X	X	X	X	X
QOL (SF-36v2, EQ5D) Forms	X	X		X	X	X	X	X
Biological tests (hematology and biochemistry, 24h proteinuria , ECBU, serology (HIV 1/2, HTLV 1/2, Hepatitis B and C) and optional viral load (HIV 1/2, Hepatitis B and C)	X	X		X	X	X	X	X
β - HCG determination	X							X
Blood gaz	X							X
X-ray and EKG	X	X				X		X
Echocardiography and, if necessary: MRI or CT scan	X							
Stomatology consultation (teeth, gums ...)	X							

Routine autoantibodies, complement proteins C3, C4 and CH50		X		X	X	X		X
Immuno-phenotyping of lymphocytes		**X**		**X**	**X**	**X**		**X**
Cytokines		**X**		**X**	**X**			
MSC immunogenicity: Detection and identification of anti-HLA antibodies + crossmatch analysis		**X**		**X**	**X**			
Daily Dose corticosteroïds	X	X		X	X	X	X	X
Cell bank		**X**		**X**	**X**	**X**		**X**
RNA bank		**X**		**X**	**X**			
Serum and Plasma bank		**X**		**X**	**X**	**X**		**X**
Evaluation of tolerance: Toxicity according to the criteria of CTCAE		X	X	X	X	X	X	X
Validation of eligibility: respect for the IC and the NIC	X							

(1) The period between eligibility and patient inclusion should not exceed four months to limit disease progression
(2) The period between inclusion and injection of MSCs shall not exceed two months

Not bold: acts of usual monitoring Boldface disease specific acts of Research **Bold:** specific acts of Research

5.7 Distinction between standard care and research

Table 9: "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 care**	**Procedures and treatments added for the study**
Patient Information and signature of informed consent	E.g. Eligibility (M-4 to D-1 before M0)	
Medical history and autoimmune disease history	E.g. Eligibility (M-4 to D-1 before M0)	
Detailed physical examination (skin, heart, lungs, skeletal muscles and joints)	E.g. Eligibility (M-4 to D-1 before M0), M0, D10, M1, M3, M6, M9 and M12	
Detailed clinical examination (date of birth, gender, weight, size, concomitant therapy)	E.g. Eligibility (M-4 to D-1 before M0), M0, D10, M1, M3, M6, M9 and M12	
SLE SLICC/ACR	E.g. Eligibility (M-4 to D-1 before M0), M0,M1,M3, M6, M9 and M12	
SELENA-SLEDAI, BILAG, SRI	E.g. Eligibility (M-4 to D-1 before M0), M0, M1,M3, M6, M9 and M12	
QOL (SF-36v2, EQ5D) Forms	E.g. Eligibility (M-4 to D-1 before M0), M0, M1, M3, M6, M9 and M12	
Biological tests (hematology and biochemistry, 24h proteinuria , ECBU, serology (HIV 1/2, HTLV 1/2, Hepatitis B and C) and optional viral load (HIV 1/2, Hepatitis B and C)	E.g. Eligibility (M-4 to D-1 before M0), M0, M1,M3, M6, M9 and M12	
β - HCG determination	E.g. Eligibility (M-4 to D-1 before M0) and M12	
Blood gaz	E.g. Eligibility (M-4 to D-1 before M0) and M12	
X-ray and EKG	E.g. Eligibility (M-4 to D-1 before M0), M0, M6 and M12	
Echocardiography and, if necessary: MRI or CT scan	E.g. Eligibility (M-4 to D-1 before M0)	
Stomatology consultation (teeth, gums ...)	E.g. Eligibility (M-4 to D-1 before M0)	
Routine autoantibodies, complement proteins C3, C4 and CH50	E.g. M0, M1,M3, M6 and M12	

Immuno-phenotyping of lymphocytes		E.g. M0, M1,M3, M6 and M12
Cytokines		E.g. M0, M1, M3
MSC immunogenicity: Detection and identification of anti-HLA antibodies and crossmatch analysis		E.g. M0, M1 and M3
Daily Dose corticosteroïds	E.g. Eligibility (M-4 to D-1 before M0), M0, M1,M3, M6, M9 and M12	
Cell bank		E.g. M0, M1, M3, M6 and M12
RNA bank		E.g. M0, M1, M3
Serum and Plasma bank		E.g. M0, M1, M3, M6 and M12
Evaluation of tolerance: Toxicity according to the criteria of CTCAE	E.g. M0, D10, M1,M3, M6, M9 and M12	
Validation of eligibility: respect for the IC and the NIC	E.g. Eligibility (M-4 to D-1 before M0)	

5.8 Biological samples

The samples that are taken during the trial (or a component of the samples, Cell, Plasma, serum, DNA,) will be stored in a biological sample bank.

As part of this research 3 biological collections will be performed:

Serum bank: from 1 dry tube of 7 ml, centrifuged at room temperature for 10 min at 3000 rpm, 2 aliquots of 0.5 ml will be obtained and will be locally cryopreserved at -80°C. They will then be stored centrally in the center of the coordinating investigator (St Louis Hospital), under the supervision of Pr J. Larghero (Cellular therapy laboratory at St-Louis Hospital, Paris).

Plasma bank: from 1 heparin tube with lithium of 4 ml, centrifuged at room temperature for 10 min at 3000 rpm, 2 aliquots of 0.5 ml will be obtained and will be locally cryopreserved at -80°C. They will then be stored centrally in the center of the coordinating investigator (St Louis Hospital) under the supervision of Pr J. Larghero (Cellular therapy laboratory at Saint Louis Hospital, Paris).

Cell bank: from gel-free lithium heparin tubes, stored at 2-5.10^6 cells per cryotube in SVF-10%DMSO in liquid nitrogen in the SITI laboratory of CHU de Rennes, under the supervision of Pr K. Tarte.

RNA bank: 2.5 ml RNA paxgene tubes will be stored at -20°C until RNA extraction. RNA will then be stored at -80°C. Paxgene tubes and RNA will both be centrally stored in the SITI laboratory of CHU de Rennes, under the supervision of Pr K. Tarte.

Samples will be anonymised according to the number of inclusion and stored in the center of the coordinating investigator of the study. Samples will be labeled with the name of the study, the first three letters of the patient's name and number inclusion, as well as sampling. The

samples will be stored and possibly used for research until 20 years after the end of the study. In case the patient does not consent, the samples will be destroyed at the end of the study.

All the biological collections will be recorded and reported to the competent authorities according to existing regulations.

- The collection of biological samples can be used for an examination of the genetic characteristics (RNA chips, PCR, sequencing ...). This can only be effective after patient's agreement by signing an informed and written consent (cf. p13 / 13 of this NIFC). The purpose of this examination is to determine if there are mutations or to identify diagnostic or risk factors.
- The collection of biological samples can be used in order to carry out retrospective or translational research on lupus disease.

At the end of the trial, the samples will be kept**.**

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

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

Table 10 : Summary table of the biological samples and collection

Type of sample	Quantity	Storage location	Manager of the sample bank	Purpose of the sample bank	Storage period	Outcome (destruction, etc.)
Serum and plasma Bank	1 dry tube of tube of 7 ml + 1 heparin tube 4 ml	Cellular Therapy Unit at Saint Louis hospital Paris	Dr Audrey Cras	Evaluation of the immunomodulatory effect on :cytokines production at M0 , M1, M3, M6 and M12.	During 20 years	Kept
Cell Bank	gel-free lithium heparin tubes	Laboratoire SITI, Service Immunologie – Bâtiment Médico-technique/hématologie clinique – Bâtiment Jean DAUSSET, CHU Rennes	Pr Karin Tarte, Dr Séverine Loisel, Joelle Dulong Cédric Ménard	Evaluation of further subsequent immunophenotyping at M0, M1, M3, M6 and M12	During 20 years	Kept
RNA Bank	2.5 ml RNA paxgene tube	Laboratoire SITI, Service Immunologie – Bâtiment Médico-technique/hématologie clinique – Bâtiment Jean DAUSSET, CHU Rennes	Pr Karin Tarte, Dr Séverine Loisel, Joelle Dulong Cédric Ménard	Evaluation of transcriptome and/or repertoire analyses at M0, M1, and M3	During 20 years	Kept

5.9 Termination and exit rules

5.9.1 Criteria and procedures for prematurely terminating the study treatment

In the interest of the patient, the investigator reserves the right to interrupt the participation of a subject under consideration in case of:

- patient presents a criterion of non-inclusion at the time of surgery
- the occurrence of an AR / EIG, compromising future assessments,
- violation of the protocol,
- withdrawal of patient consent,
- patient lost to view,
- non-compliance of the UC-MSC.

5.9.2 Different situations

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

The investigator must:

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

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

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

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

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

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

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

5.9.4 Monitoring subjects after the premature termination of treatment

If a subject exits the study prematurely, all data, scores and evaluations before the release date of the patient will be collecting into CRF and monitored for the primary endpoint, secondary endpoints and safety assessment.

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 3 months (to be determined by the investigator) following the premature termination of treatment (to be adapted depending on the study). If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI 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.
The serious adverse reaction will be monitored until it is resolved.
If a Data Monitoring Committee has been created, the committee can specify and/or validate the monitoring methods.

In case of premature discontinuation of treatment:
Any undesirable event concerning you will be immediately taken care of in the medical and paramedical way in the UF04 department of Internal Medicine, Auto-Immune Diseases and Vascular Pathology of Pr Farge of the Hospital (AP-HP) Saint Louis in Paris adapted until 'to its complete resolution with return to the previous state or stabilization at a level considered acceptable by the investigator.

In the case of a premature termination of the research:
because of your toxicity or concerning another patient, the promoter will gather as soon as possible the members of the Independent Surveillance Committee (CSI), which in their function of expert, analyze the severity of the adverse event and advise on whether or not the trial should be closed. Following this opinion of the CSI, the promoter, the sole decision maker, will decide on the premature termination of the Research.
In case of premature termination of the research, you will immediately be informed directly by the investigator of the decisions taken by the sponsor and will be followed as part of the usual care of your disease even after premature termination of the research.

5.9.5 Full or partial cancellation of the study

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

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed or if there is a discrepancy in the serious adverse reactions, requiring a reassessment of the benefit-risk ratio for the trial.
- if an interim analysis confirms the efficacy of the treatment arms or, alternatively, the lack of efficacy**.**
- 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 UC-CSM, in light of which the objectives of the study or clinical programme are unlikely to be achieved.
- AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

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

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Patient :

1- Age > 18 years and < 70 years.

2- Diagnosis of Systemic Lupus Eythematosus (SLE) according to the ACR criteria with positive antinuclear antibodies.

3- Subjects with sustained disease activity defined by a SELENA- SLEDAI SLE activity index ≥ 6 at baseline,

4- Inefficacy or adverse effects necessitating discontinuation of first and second line therapies of SLE including:

c. Prednisone orally ≥ 6 mg / day (or equivalent) for at least 28 days.

d. At least one or more of the following immunosuppressive therapies for 3 months in total:

i- Cyclophosphamide, iv bolus ≥500 mg / month for 3 months minimum

ii- Mycophenolate mofetil, orally or equivalent at a dose≥ 2000 mg / day for at least 90 days

iii- Azathioprine orally at a dose≥ 2 mg / kg / day for at least 90 days;

iv- Methotrexate orally or parenterally, at doses ≥ 20mg / week for at least 90 days;

v- Leflunomide orally, at a dose of≥ 10-mg / day for at least 90 days;

vi- Rituximab (anti-CD20) intravenous bolus 375 mg / m2, once a week for four weeks or total dose of 1 g twice a day for two weeks

vii- Cyclosporine orally, at a dose of 2.5-5 mg / kg / day, for at least 90 days;

viii- Belimumab intravenously or subcutaneous at monthly bolus of 10 mg / kg infusion), for at least 3 months.

5- Patient who received treatment of SLE at stable doses for a minimum of 30 days prior to eligibility, including one of the following treatments: prednisone (or equivalent) alone or combined with antimalarial treatment, an anti-inflammatory steroidal and / or an immunosuppressant.

6- Negative pregnancy test for women of childbearing age.

7- For men and women : Using effective contraceptive methods during treatment and within 3 months after the end of treatment for men with her partner of childbearing age

8- Signed Informed Consent.

9- Affiliation to social security.

6.2 Exclusion criteria

1. Pregnancy, breastfeeding or lack of contraception adapted for the duration of the study.
2. Presence of severe (s):
    a) Renal insufficiency: calculated creatinine clearance of <30 ml / min
    b) Altered cardiac function: clinical signs of congestive heart failure; left ventricular ejection fraction <40% on echocardiography; uncontrolled ventricular arrhythmia;
    c) Hepatitis defined by abnormal levels of transaminases (AST, ALT> 2 times normal) not related to disease activity.
    d) Respiratory disease: mean PAP> 50 mmHg (echocardiography), respiratory failure defined by a resting blood pressure of oxygen at PaO 2 < 70 mmHg and / or PaCO2 > 50 mmHg without oxygen
3. Severe psychiatric disorders, including severe psychosis related to SLE, which would prevent to give informed consent or to undergo the procedure.
4. Active neoplasia or concomitant myelodysplasia, except for basal cell carcinoma or squamous cell carcinoma or in situ cervix carcinoma.

5. Bone marrow failure defined by neutropenia <0.5.10^9/L, thrombocytopenia <30. 10^9 / L, anemia < 8 g / dL lymphopenia CD4 + <200 x 106 / L caused by another disease than SLE.
6. Acute or chronic uncontrolled infection: HIV 1/2, HTLV-1/2, Hepatitis B (AgHBs), Hepatitis C with positive PCR (optional PCR)
7. Patient having received belimumab intravenously or subcutaneous within 2 months of Baseline, or having received rituximab or other B cell depleting biologic therapy within 6 months of Baseline
8. Current substance abuse or recent (within 60 days) history of substance abuse
9. Patient in periods of exclusion from the national roster of researchers
10. Patient with Linguistic or psychological incapacity to sign informed consent
11. Patient already included in another study at the same time.
12. Risk of poor patient compliance.
13. Patient under legal protection.

6.3 Recruitment methods

The SLE patient's recruitment will be done by the Investigator Site in the case of standard hospitalization and by FAI2R network. The Internal Medicine service of the Reference Center for Lupus at Civil Hospital of Strasbourg (Pr T.Martin), the Internal Medicine Service at PURPAN Hospital,University Hospital of Toulouse (Dr G. Pugnet) and the National Reference Center of Rares and Systemic Auto-Immunes Diseases, Lupus and antiphospholipid antibody syndrome, Vasculitis, Myositis, Gougerot Sjögren, Polychondritis, Immunological thrombocytopaemia, Sarcoidosis, Sharp, Still, Clarkson at E3M Institut La Pitié Salpêtrière-Charles Foix - Pitié-Salpêtrière Hospital (Pr Z. Amoura) will only address patients to the Investigator Site (Pr Farge).

Announcements and advertisements will be given in the form of a poster that will be given to the Investigator site (UF04 Internal Medicine service) and all associated centers of this protocol and "Association Française du Lupus et autres maladies auto-immunes" (AFL+ association).

Severe SLE patients will be selected by the clinical investigators who will inform the patients about the risks, constraints and potential benefits in her (his) participation to this research. The patient will have the necessary time for own decision and after information decision.

a) Recruitment strategy and Pre-screening

The recipients will be selected at the investigator site. After being informed of the study, an eligibility assessment will be performed for recipients, which details are presented below in the examinations table. Once included, the recipient patient will be monitored every 3 months for 1 year. To assess the potential inclusion of patient to participate in this research, a review of eligibility criteria will be performed and the investigator will then collect the patient signed informed consent.

b) Inclusion

The patient will be considered included in the research if all the inclusion and the exclusion criteria are respected, especially with regard to the results of the eligibility assessment.
The investigator will inform the patient of his inclusion or his non-inclusion in the study. The date of inclusion as well as the transmission of information to the patient will be recorded in the medical file.
The inclusion will be saved by the clinical research unit (URC) at Saint-Louis Hospital DBIM and sent to the Cellular Therapy Unit (CTU) at UCL (Pr Lowdell) and at St Louis hospital (Pr Larghero) within 24 to 48 h after the patient effective inclusion.

Table 11 : Summary table of the recruitment subjects per site and per month

	Number of subjects
Total number of subjects to be included	10
Number of sites	1
Enrolment period (months)	42
Number of subjects/site	10
Number of subjects/site/month	**0,2**

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 The investigational medicinal product(s)

7.1.1 Investigational medicinal product

7.1.1.1 Characteristic and supply

The final product consists of allogeneic MSCs from umbilical cords (UC-CSM) suspended in 0.9% NaCl solution containing 10% of 5% albumin and in concentration ≤ $2x10^6$ CSM/mL. The maximum final volume is 20 mL / kg of recipient weight.
Initially 5 subjects at the initial dose of 2.10^6 UC-CSM/kg recipient weight will be included.
The following 5 subjects will be enrolled in a dose:
- 1.10^6 MS /kg there is a high probability of excessive toxicity at 2.10^6 MSC / kg;
- 4.10^6 CSM/kg if there is a low probability of excessive toxicity 2.10^6 CSM / kg

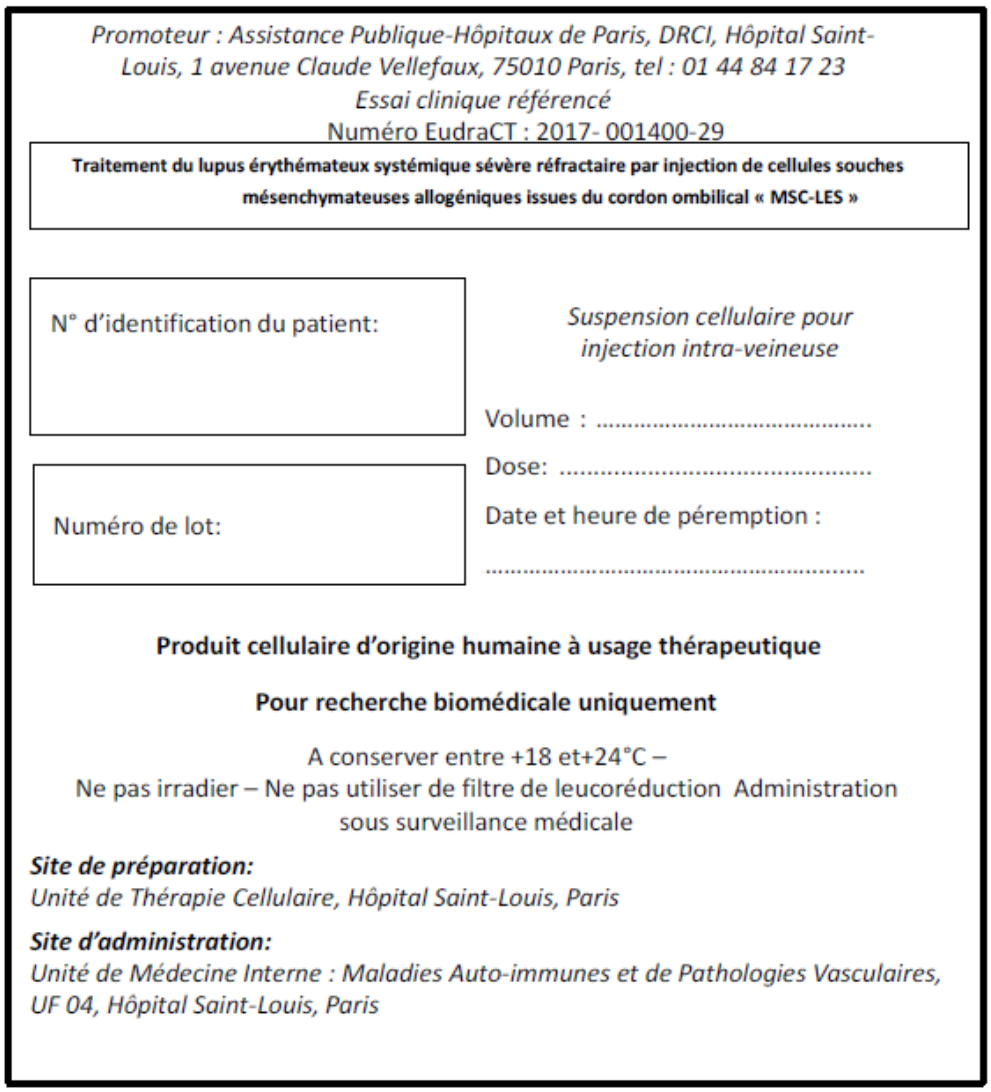
UC-CSM will be administred by 1 injection during 30min to 1h by Intravenous infusion.
Primary and secondary packaging, labelling, storage conditions are described below (see Medicinal drug product label):

7.1.1.2 Packaging

Working Cell Stock packaging (see IMPD):
WCS cells are cryopreserved inside 50 ml cryopreservation bags with a maximum fill volume of 20 ml using a controlled rate freezer. These bags are made of clear Ethylene Vinyl Acetate (EVA) tubular film. The freezing bags are equipped with extra-long EVA tubing for drawing quality control samples out of heat-sealed tube sections. The tubing is provided with luer connectors, roller clamps, and an injection port. The EVA tubing and injection port are DMSO-resistant. Two ports with sealed, twist-off protective caps minimize the risk of nitrogen ingress into these ports.
CryoMACS Freezing Bags are manufactured by Miltenyi Biotec GmbH and controlled under an ISO13485 certified quality system. These products are available in Europe as CE-marked medical devices. CryoMACS Freezing Bags are for cryopreservation applications at ultra-low temperatures and intended for a single cycle of freezing, storage (down to -196°C), and subsequent thawing (at 37°C). All bags will also be vacuum packed in a secondary plastic bag.

Final Drug product packaging (see IMPD):
The cells will be contained in a CE marked sterile bag labelled (see Appendix 3) and placed in a plastic pouch (secondary container). The shipping package consists on a transport box (third container) for human biological products.
The stability of the finished product has been evaluated in the final bag for 4 hours at room temperature (21°C) (Table 19).

Medicinal drug product label



7.1.1.3 Conditions of storage and use

The cell therapy medicinal product is not stored prior to administration. After the release, the product will be immediately distributed to the clinical unit for administration. Transport will be performed between +18 and +24°C in a sealed container. The duration of the transport is approximately of 10 minutes and will be performed by a technician lab from the cell therapy unit from Saint-Louis hospital (see IMPD).

Release Criteria for the cell therapy medicinal product **(see IMPD table 17 p30) :**

Description	**Method**	**Release criteria**
Cell count	Haemacytometer	= cell dose/kg patient
Viability	Flow cytometer	≥ 80%
Immunophenotype	Flow cytometer	CD90+ ≥ 90% CD73+ ≥ 90% CD105+ ≥ 80% CD45+ ≤ 5%
Sterility *	Automated CO_2 detection	Absence of germs

*Results will be obtained 10-day after administration to the patient. In case of positive results occurring, the identity of bacterial strain and antibiogram will be transmitted to the clinician in order to implement an adapted antibiotic treatment.

There is a process for exceptional release in the event that release specifications are not met (under conditions which do not exceed 10% of the specifications). Release of non-conforming products is performed with notification and accordance of physician.

For lots not meeting the criteria:

The number of cells before the release of the batches must be at least equal to the prescribed quantity which is a function of the dose level and the weight of the recipient. A minimum quantity of 100x106 cells is expected by Professor Mark Lowdell's CCGTT production centers

If the specifications of the final batch to be released were not met, in terms of cell number, cell viability, or phenotype (% CD90 +, CD73 +, CD105 +, CD45 +), the clinician may apply for a written dispensation The lots may be released only in the case of a variation not exceeding 10% (see p.23 of the technical file or IMPD in force). The proponent must be informed of any such derogation either by the clinician or by the production center.

The batch can not be released in case of not meeting release criteria (over 10%), technical problems or contamination during the 4 days-culture of the final product. It is to be noted that an another bag of WCS will be used by the UTC, in order to have the possibility to prepare an another batch for the patient for its treatment.

- Non-release specifications:

Description	Method	Information
CFU-F	Culture assay	Presence of colonies
Karyotype	Standard G-banding karyotype	Normal at least 20 mitoses

If one of the non-release specifications is not met, the UTC shall notify the proponent.

7.1.1.4 Preparation for Administration

The final product consists of allogeneic MSCs from umbilical cords (UC-CSM) suspended in 0.9% NaCl solution containing 10% 5% albumin and in concentration ≤ $2x10^6$ CSM/mL. The maximum final volume is 20 mL / kg of recipient weight.
Initially 5 subjects at the initial dose of 2.10^6 UC-CSM/kg recipient weight will be included.
The following 5 subjects will be enrolled in a dose:
- 1.10^6 MS /kg there is a high probability of excessive toxicity at 2.10^6 MSC / kg;
- 4.10^6 CSM/kg if there is a low probability of excessive toxicity 2.10^6 CSM / kg

UC-CSM will be administered by an intravenous perfusion during 30min to 1h.
Primary and secondary packaging, labelling, storage conditions are described below (see above Medicinal drug product label).

A minimum delay of one month between the inclusion of 2 patients within the trial will be observed.

7.1.2 Traceability information for the investigational medicinal product(s)

UC-MSCs are delivered in Investigator site (UF04 Internal Medicine service) with:
- a validation certificate of finished product specific for each patient summarise the patient's identity, patient's weight, date and location of collection, the harvest time, the time of expiration, the UC-CSM dose, the results of quality control, specifications and the

conformity of the investigational medicinal product, the responsible of release..

- a specific transport and tracability sheet specific for each patient that resumes the number and date of birth of patient's inclusion, the date and hour of distribution, the Batch number, the concentration and volume of plastic bag, the sender and the receiver of the transport, the responsible of transport and the date, hour, results and conformity of transport, the responsible for the traceability for the investigator site.
- an injection sheet to ensure the traceability of administration (responsible, date, time, duration of injection and adverse effects during injection) accompanied with an injection instructions for investigator site)

This protocol is accompanied the Circuit of the Cell Therapy product (see Appendix 17).

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

Authorised treatments:

- prednisone (ex: Cortancyl) used per os In the form of the tablets which will be swallowed with a little water, during the meal. Dosage will be defined in the form of the disease progression for each patient.
- Polaramine, necessary treatment for carrying out the research, used during the conditioning regimen, solution for injection
- Treatment by prednisone is not the only treatment allowed during the trial. In fact, after the patient has been included, in the case of SLE aggravation, all available treatments can be administered. All treatment drugs will be identified in the CRF (date of administration and dosage). Immunosuppressive treatments taken prior to the injection of MSCs and those not responding to the inclusion criteria 4 " Inefficacy or adverse effects necessitating discontinuation of first and second line therapies of SLE including " may be continued.

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

Clinic and biological follow-up every 3 months after MSC injection as previously described.

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

Clinical and biological parameters will be collected at Day 10, at one month and then every 3 months during patient's regular follow-up for 1 year: M0, M1, M3, M6, M9, and M12 with the analysis of all SLE index as previously described.

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Steering Committee

- Operating procedures:

The role of this Committee is to define the General organization of Research, coordinate information, initially determine the methodology and ensure the proper conduct of research. It may propose lines to keep during the Research, taking note of the recommendations of the Independent Monitoring Committee independent as appropriate. The ERD decision-making rest proponent.

The Committee will consist of:

Investigator site members:

- **Pr Dominique FARGE-BANCEL,** head of the unit of internal medicine pathology vascular, Saint-Louis Hospital, Paris,
  Role in this Research: Coordinating investigator

- **M. Damien VANHOYE,**
  Role in this Research: Clinical Research Manager in Investigator Site.

- **Ms. Eola FRANCIUS**,
  Role in this Research: Hospital Clinical Research Assistant in Investigator Site.

CTU St Louis members:

- **Pr Jérôme LARGHERO,** Director of cell therapy unit, Saint-Louis Hospital, Paris
  Role in this Research: Responsible for release of final product (UC-MSC)

- **Dr. Audrey CRAS,** Cell processing facility director, cell therapy unit, Saint-Louis Hospital, Paris
  Role in this Research: Responsible for production of final product (UC-MSC).

UCL members:

- **Pr Mark LOWDELL**, Director of cellular Therapeutics and RFH/UCL, London, UK

Role in this Research: Responsible for the production and release of the drug substance at UCL

DRCI/APHP sponsor members:

- **M. Damien VANHOYE**, Clinical Research Manager of DRCI Saint-Louis Hospital, Paris, France

Role in this Research: Clinical Research Manager, responsible for the Good Research Progress in the respect of Reglementary Rules and deadlines following the Good Clinical Practices.

- **Dr Matthieu RESCHE-RIGON,** Biostatistician, Department Biostatistics and medical informatics (DBIM) of the Saint-Louis Hospital, Paris;

Role in this Research: Biostatistician

- **El Mountacer EL ABBASSI** : Clinical Project Manager, Clinical Research Unit, Saint-Louis Hospital, Paris, France

Role in this Research: Clinical Project Manager

- **Marine COGNAT :** Coordinator of Clinical Research, Clinical Research Unit, Saint-Louis Hospital, Paris, France

Role in this Research: Coordinator of Clinical Research

Operating procedures: Meeting once a month to:

- define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
- 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)

Cf part 10.3.6

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

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

Adverse side effects will be coded according to the medical activities regulatory dictionary (version 12.0) classified by organ system and severity of an adverse event using tables of classification on the severity of the adverse effect, which were changed from the National Institute of Allergies, of the Division of adult infectious diseases of microbiology and the toxicity of adult infectious diseases.

10.2 Recording and reporting adverse events

10.2.1 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**

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 sponsors of clinical trials conducted on investigational medicinal product (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.

10.2.2 The 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 (CRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:
- either general terms:
  - Mild: tolerated by the patient, does not interfere with daily activities
  - Moderate: sufficiently uncomfortable to affect daily activities
  - Serious: preventing daily activities
- or a severity grading scale for adverse events, based on CTCAE criteria and WHO toxicity, attached to the protocol (Appendix 13) :
  - Common Terminology Criteria for Adverse Events (CTCAE, V4.03 of June14, 2010, U.S. Department of Health and Human Service) [National Cancer Institute]
  - WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product UC-MSC .

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 12: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)

Causality term	Assessment criteria*
	· Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

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

10.2.3 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 and, if applicable, in the investigator's brochure as not requiring a notification without delay.

A serious adverse event is any untoward medical occurrence that:

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

The serious adverse events are those associated with a serious progression of the disease as demonstrated by:
- the increase of the BILAG score from E to A compared to the value at the baseline
- ≥ 25% decrease in FEVG (left ventricular ejection fraction): heart failure, tachycardia, dyspnea, edema, edema syndrome
- the fall ≥ 20% of the weight of the patient
- renal impairment: ≥ 30% decrease compared to baseline creatinine value.
- organic insufficiency, septicemia, infectious complications with deterioration of the patient compared to the inclusion
- deep cytopenia (CTCAE grade 3 or 4)

Theoretical and unforeseen risks considered by the promoter (reported to the ANSM by the promoter):
- Possible occurrence of a severe allergic reaction within 12-24 hours after MSC administration and potentially linked to an exogenous protein in the cell suspension fluid (human albumin)
- Secondary neoplasia

10.2.4 Specific features of the protocol

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

- Adverse events judged as being "medically significant"

- the increase of the BILAG score from E to A compared to the value at the baseline
- ≥ 25% decrease in FEVG (left ventricular ejection fraction): heart failure, tachycardia, dyspnea, edema, edema syndrome
- the fall ≥ 20% of the weight of the patient
- renal impairment: ≥ 30% decrease compared to baseline creatinine value.
- organic insufficiency, septicemia, infectious complications with deterioration of the patient compared to the inclusion
- deep cytopenia (CTCAE grade 3 or 4)
- thromboembolic events

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

- Serious adverse events of particular interest (ANSM declared by the sponsor):

Any organic deficiency, septicemia (≥ 3 according to CTCAE), infectious complications (≥ 3 according to CTCAE), deterioration of the patient's condition with respect to the inclusion and requiring a passage of resuscitation

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

- **Potential severe complications due to Mesenchymal Stem Cells**

Neoplasia

- **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.

- Exposure **via breastfeeding**

Exposure via breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure via breastfeeding.

10.2.4.2 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 (CRF). ACRF extraction of these serious adverse events will be realized every 3 months.

- Normal and natural course of the condition:

  - BILAG score increase from E to A with respect to the value at baseline
  - fall <25% LVEF (Left Ventricular Ejection Fraction)
  - fall <20% of the patient's weight
  - Renal impairment: fall <30% compared to the value of creatinine at baseline.
  - scheduled inpatient hospitalisation for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]
  - inpatient hospitalisation for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition

- emergency inpatient hospitalisation upon enrollment or prolongation of hospitalisation upon enrollment for monitoring the condition under investigation
- worsening of the condition under investigation

Special rules for trials with a high mortality rate (e.g. morbidity/mortality studies whose primary endpoint is mortality; trials conducted in an emergency setting upon patient enrolment; low risk trials conducted in a patient with a high mortality risk):
The primary objective of the trial is to assess the tolerance of allogeneic umbilical cord derived MSC administration for severe SLE refractory to standard therapies (cyclophosphamide mycophenolate mofetil and corticosteroids with or without anti CD20).
The mortality rate of the condition under investigation is 10% at 10 years [14].
These data will be sent to the Data Safety Monitoring Board members every 3 months.
If there is any imbalance between the mortality rate is higher than expected (1% per year) for 5 patients affecting the safety of trial subjects and which requires the sponsor to take urgent safety measures, the ANSM will be informed about the emerging safety issue without delay.

- Special circumstances
  - Hospitalization for a pre-existing illness or condition
  - Hospitalization for a medical or surgical treatment scheduled prior to the trial
  - Admission for social or administrative reasons
  - Transfer to the emergency ward (< 12 hours).

- Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care

The investigator must report these events to his Centre Régional de Pharmacovigilance (CRPV).

- *Adverse events during the trial possibly related to treatments/acts prescribed as a part of the patient's standard care*

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

10.2.4.3 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, except those listed in the investigator's brochure as not requiring for notifying the sponsor:
- starting from the date on which the subject begins treatment with the investigational medicinal product (UC-MSC)
- throughout the whole follow-up period intended by the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product (UC-MSC) or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

10.2.4.4 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. 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 completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI 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 CRF

- the investigator completes the SAE report form, then validates, prints and signs the form before sending it by fax or by email;

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.

10.2.5 Procedures for reporting biovigilance to the sponsor

10.2.5.1 Définitions

According to Article R12-31 of the French Public Health Code:

- **Incident** : Accident or error related to the activities relating to the elements, products or derivatives mentioned in item 1 of I of article R. 1211-29 resulting or likely to result in:
  a) An adverse reaction in the persons mentioned in item 30 (I) of Article R. 1211-29;
  b) A loss of the element, product or derivative;
  c) A defect in the quality or safety of the element, product or derivative.

- **Serious incident** :

a) Any incident causing or likely to result in:
- a serious adverse reaction or an unexpected adverse reaction in the persons mentioned in item 30 of I of Article R. 1211-29;
- any significant loss of the element, product or derivative preventing the graft from being performed or the administration of the product;

b) Any unusually high incidence of incidents or expected adverse reactions;

c) Any information concerning the donor or the donation, discovered incidentally after collection and the consequences of which are likely to entail a risk to the health of patients and recipients.

10.2.5.2 Obligation of health professionals (investigator, "Correspondant Local de Biovigilance", producer or head of cell therapy unit)

Any health professional who is aware of a serious incident must report it to the sponsor without delay as soon as he becomes aware. It may be the investigator, the producer, the head of Cell Therapy Unit or the "Correspondant Local de Biovigilance" (CLB). It complements the specific section of the observation booklet (CRF).

In case of a serious incident, the health professional completes the biovigilance form (see appendix 3 to the protocol) and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI 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.

In all cases, it is not necessary to have all the elements expected in the investigation of the incident or adverse reaction to report to the sponsor. Additional information will be sent further as necessary.
Any useful documents (hospitalization report, batch release form, chimerism results) should be forwarded to the sponsor whenever possible.

If the sponsor requests additional information, the "Correspondant Local de Biovigilance" or other health professional in his / her absence shall carry out the appropriate investigations and inform the sponsor of the results of the investigations.

The "Correspondant Local de Biovigilance" will be responsible for reporting to the Agence de la Biomédecine ((French health competent authority for biovigilance)) any serious incidents and for informing potentially affected health professionals (other CLBs in other institutions, vigilant in Other fields ...).

10.2.6 Role of the sponsor

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

10.2.6.1 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 investigational medicinal product and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **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 if the product is not authorised, 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 to the investigational medicinal product Allogeneic Umbilical Cord derived-MSCs (UC-MSC):

- refer to the Investigator's Brochure version 2.0 of 03/06/2019.

The serious adverse events associated with the study procedures are:

- risks related to the examinations (cf part 2.8)
- serious adverse events likely to be related to immunosuppressive therapies : refer to the SmPC for mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate, leflunomide, ciclosporin, belimumab.

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 adverse effects occurring in the donor and serious incidents without delay as soon as the sponsor becomes aware.**

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

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

"Reporting requirements for these serious adverse events associated with a serious progression of the disease demonstrated by:

- the increase of the BILAG score from E to A compared to the value at the baseline
- ≥ 25% decrease in FEVG (left ventricular ejection fraction): heart failure, tachycardia, dyspnea, edema, edema syndrome
- the fall ≥ 20% of the weight of the patient
- renal impairment: ≥ 30% decrease compared to baseline creatinine value.
- organic insufficiency, septicemia, infectious complications with deterioration of the patient compared to the inclusion
- deep cytopenia (CTCAE grade 3 or 4)

The sponsor must notify the initial report to the national competent authority within 48 hours, working days starting from the moment the sponsor is informed of these serious adverse events without delay upon receipt if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of these serious adverse events. The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt."

Specific rules for serious adverse events of special interest:
The sponsor may be required to declare serious adverse events of special interest, with the same procedures and within the same timelines as for SUSARs.

10.2.6.2 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.
[Include or delete the following paragraph as applicable] For the clinical trials involving the first administration of a medicinal product in healthy volunteers, emerging safety issue is defined as all serious adverse reactions occurring in trial subjects.

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.

10.2.6.3 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) 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 authorization of the clinical trial by ANSM.

10.2.7 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.

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

A DSMB will be convened for this biomedical research because this is studie where study risk level is "D". The DSMB will hold its preliminary meeting before the first inclusion of the first patient.

General information about the DSMB: The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research, but the sponsor remains the only decision maker. The recommendations that the DSMB can make are:

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

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one specialized clinician in the pathology being studied and one specialist in the studied medication being studied (or a pharmacologist/pharmacovigilance

specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. The DSMB must hold its preliminary meeting before the first inclusions of the first patient and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

Definition of the DSMB's missions:

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

Definition of the DSMB's operating methods:

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

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

The DSMB of the study consists of the following way:

Table 13 : Summary table of DSMB's members :

Name	Address / phone/mail	Specialty
Pr Jacques Eric GOTTENBERG **(Chairman of the committee)**	Hautepierre Hospital Avenue Molière - BP 83049 - 67098 Strasbourg **Tel : 03.88.12.79.54** Email : ***jacques-eric.gottenberg@chru-strasbourg.fr***	Rheumatology

Pr Marie Thérèse Rubio	CHU de Nancy – Bradois Hospital Hematology service 5 rue du Morvan 5411 Vandoeuvre-Les-Nancy **10.2.8** Tel : 03 83 15 32 82 Email : m.rubio@chru-nancy.fr	Hematology
Dr Christophe DELIGNY	CHU ZOBDA-QUITMAN FORT DE France **Tel : 04 76 76 89 60** Email : ***christophe.deligny@chu-fortdefrance.fr***	Médecine Interne

The first meeting of the DSMB was held **before the inclusion of the first patient in the research, on May 19, 2017.** The Chairman of the Committee was appointed in the person of Jacques Eric Gottenberg, the and modalities of operation have been defined and are described in the Charter for the maintenance of the DSMB of the study ("*v1.0 du 19/05/2017 revu le 22/11/2017*").

Records of the meetings of the DSMB will be sent regularly to the ANSM.

The following safety rules have been validated:

- **Provisional suspension criteria for inclusions**
  - Death, setting life-threatening, or occurring of all SAE, SUSAR, or new fact likely to be due to the experimental treatment.
  - Severe SLE outbreaks likely to be attributable to experimental treatment.
  - If appropriate, the sponsor will consult the Committee for an opinion.
  - Deep Cytopenia (grade 3 or 4 to CTCAE)
- **Passing criteria to the level of higher doses**
  - The 5 first patients will be all included in the dose of 2.10^6 cells/kg of the weight of the receiver, then an assessment of tolerance **after the M3 from 5 patient will be done**. The latter will be conducted by the Biostatistician of the study, according to stopping Bayesian rules, in accordance with what is described in the chapter 9.3 of the Protocol into force.
  - The sponsor will collect the opinion of the IOC, prior to its decision to stop the inclusions, decrease the dose or to increase it in the light of the results of this analysis.

10.2.6 Description of the potential risks and expected adverse effects on the basis of the available data.

a) Expected non-serious adverse effects:

- Related to the pathology and its evolution Progression of the disease with an aggravation, considered like non-significant, of activity scores,

- Related to the injection of cell therapy: redness at the injection point, Flush, pain to the injection point, thrill/hyperthermia, dyspnea, chest pain, Erythema, blood pressure/pulse modifications. In the case of a reaction during the injection, the administration will be interrupted. A biological assessment of the patient will be realized to the Research looking for arguments in favour of hypersensitivity (count looking for a elevated eosinophils values, determination of circulating histamine and plasmatic trypstase). Therapeutic support of the allergic reaction, where appropriate, will depend on the severity and according to the international recommendations (Soar J, Resuscitation, 2008).

b) Expected serious adverse reactions:

- link to the evolution of the pathology and defined as**:**

Disease progression objectified by A BILAG in more than 3 domains and correlated with the occurrence of at least one of the following criteria:

- Occurrence of clinical or biological or radiological signs evocative of a malignant transformation or neoplasia.
- Any complications involving setting life-threatening of the patient, not explained by the natural evolution of the lupus disease.

(See: notification of the SAE grid in annex 3 and latest version in force of the investigator's brochure version 2.0 of 03/06/2019).

11 DATA MANAGEMENT

11.1 Data collection

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

All the data will be transcribed on the case report form (CRF). All information required by the protocol must be provided in the case report form and an explanation given by the investigator for each missing data. The data will be transferred to the case report form as and when they are obtained, whether clinical and para clinical data. Moreover, the collection of all immunosuppressive or immunomodulating drugs will be monitored. Wrong screened data on the case report form will be replaced on the CRF by declared investigator. The anonymity of the patients will be insured by the mention maximally to the number in the research, the initials of the name and first name of the person undergoing research on all necessary documents to the research, or by deletion by appropriate means (white-out...) of personal data on the copies of source documents, for the documentation of the research. The file of computerized data will be declared to CNIL under the procedure suited to the case. The CRA, the Project Manager of DRCI, the Project Assistant of DRCI, the Coordinator of Clinical Trials of CRU and the Clinical Data Manager of the research will have the possibility to view the CRF.

11.1.2 Right to access source data and documents

11.1.2.1 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)

11.1.2.2 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.

In the case of this Research, the source documents are list in the medical file of the patient where we find:

- Biological Results,
- IRM, EKG, echocardiography, radiography results and reports,
- Medical observation from the practitionners,
- Patient reports who cames for consultations, for day hospitalization, for a complete hospitalization.

11.1.2.3 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.

11.2 Data processing and storage of documents and data

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

The research will be framed according to the standard operating procedures of the sponsor. The conduct of research in study centers and support for patients will be made in accordance with the Helsinki declaration and the usual good practices.

The Coordinating Investigator and Hospital Clinical Research Assistant from UF04 Internal Medicine at Saint Louis Hospital will be responsible for data entry and the relevant procedures. The Biostatistician, Department Biostatistics and medical informatics (DBIM) of the Saint-Louis Hospital, Paris;will be conducting the statistical analysis.

11.2.3 Data entry

e.g. Paper CRF : Data will be entered in duplicate in anonymised data entry forms. This will be done by dedicated Research personnel, Hospital Clinical Research Assistant and the Coordinating Investigator.

A register of eligible patients will be required separately. Contact information's of the patients will be kept in the medical file, but will not be saved in the computerized database. All

information required by the protocol must be provided in the Case Report Form and an explanation given by the investigator for each missing data.

The data must be transferred in the CRF as they are obtained, whether it is clinical or paraclinical data. The data must be copied from a net and readable manner in black ink in these CRFs (this is to facilitate duplication and computer input). Detected erroneous data on the Case Report Form will be clearly barred and new data will be copied on the CRF with the initials and the date by the member of the investigator's team who made the correction.

The anonymity of the patients will be insured by a code number and the initials of the person who lends itself to the research on all the documents necessary for the research, or by deleting by appropriate means of personal data on copies of source documents, intended for documentation of the research.

Computerized data on a file shall be declared to the CNIL under the procedure adapted to the case.

11.2.4 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) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy.

This change was approved in a decision made on 5 January 2006. AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method". The DRCI must be informed of all project of amendment of protocol by the coordinating investigator.

The amendments should be qualified in substantial or not. A substantial modification is a likely modification, one way or another, to modify the guarantees provided to persons who lend themselves to the biomedical research (modification of an inclusion criteria, extension of duration of inclusion, participation of new centers,...).After the beginning of the research, any substantial modification thereof at the initiative of the sponsor shall obtain, prior to its implementation, a favorable opinion of the Committee, and an authorization of the competent authority. In this case, if necessary, the Committee insures that a new consent from persons involved in the research is well collected. Furthermore, any extension of the research (deep change in the regimen or included populations, extension of treatment and or therapeutic acts not originally provided in the Protocol) should be considered as a new research.

11.2.5 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 **20 years** after the end of the trial.

This indexed archiving includes, in particular:

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

- the enrolment list or register
- the appendices specific to the study
- the final study report

- The data collection documents

11.2.6 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

Statistical analysis will be conducted by Pr Matthieu Resche-Rigon, from the Clinical Research Unit of St Louis-Lariboisière Hospital group, after Data collection and quality control.

Statistical analysis will be performed **sequentially**, after observation of the main criterion (i.e., the proportion of patients in whom the procedure is not tolerated at dose 1 x 10^6 MSC per kg of weight of receiver, i.e., up to 10 days maximally after inclusion) of each included patient. It is to estimate the probability of intolerance using a Bayesian, from a beta-binomial model approach [51, 111]. The Bayesian approach is to consider the rate of intolerance (p) as a random, centered priori density variable on the expected rate of immediate intolerance (20%), which will be updated sequentially as the observations into a so-called law a. ex post

Priori density will be chosen in the family of combined laws Beta, defined by its two parameters a and b (with a hope = $\frac{a}{a+b}$ and a variance = $\frac{ab}{(a+b)^2(a+b+1)}$). The Bayes of intolerance rate estimator will be hope of the act retrospectively, i.e., the Beta of the parameters Act has A_n et B_n, defined from those of the prior Act and the number of n inclusions, as follows : A_n=a+r et B_n=b+n-r, where r is the number of tolerance observed included n. We have the following estimator: $E(\pi|r,n)=\frac{a+r}{a+b+n}$.

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

10 patients range are included in this test using a Bayesian approach.

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

NA

12.4 Anticipated level of statistical significance

12.5 Statistical criteria for termination of the study.

Stop Bayesian rules will be calculated sequentially and after the inclusion of the first 5 patients at the dose of 2 x 10^6 MSC per kg of weight of receiver, to eventually take a decision to stop the inclusions and/or increase (4.10^6 MSC per kg of weight of receiver) or decrease (1.10^6 MSC per kg of weight of receiver) dose from the two following criteria [43]:

Criterion 1 = probability a posteriori intolerance π rate is greater than 20% (the threshold of intolerance considered)

Criterion 2 retrospectively = probability that the rate of intolerance π is less than 20% (the threshold of intolerance considered)

Judgment decisions are as follows:

If **criterion 1** > 0.70: judgment of inclusions at this dose and reduction dose for 5patients, following

If **criterion 2** > 0.70: judgment of inclusions at this dose and increase the dose for 5patients following

The main motivation for choosing a sequential and Bayesian strategy was to provide continuous monitoring of the results throughout the trial and to ensure patient protection from overly toxic treatment. As the results of the patients in the trial are recorded, the posterior distribution of the probability of toxicity will be updated by applying the Bayes theorem. Depending on this later distribution, criteria can be used to modify the doses administered.

The choices of the different thresholds are the results of discussions between the clinicians involved in the study and the methodologists in charge of the design of the study. The starting hypothesis is that the increase of the dose potentially implies an increase of the expected effect but also of the toxicities. It was considered that considering the pathology, complications of other treatments and the expected toxicities following stem cell injection a maximum of 20% intolerance / toxicity was reasonable.

Let πt be the probability of intolerance / toxicity, criterion 1 corresponds to the a posteriori probability that the intolerance rate πt is greater than 20%, ie P ($\pi t > 0.2$); Criterion 2 to the a posteriori probability that the intolerance rate π is less than 20%, ie P ($\pi t < 0.2$). It was decided to take a threshold ensuring easily a de-escalation of doses in case of suspicion of possible on toxicity. So as soon as this P ($\pi t > 0.2$)> 0.7 the dose of stem cells is decreased. The usual thresholds for stopping or falling rules are usually higher (around 0.9; Yao, B., Zhu, L., Jiang, Q., & Xia, HA (2013). Clinical trials, Pharmaceutics, 5 (1), 94-106.) "; But the choice of a lower value quickly avoids the risk of exposure to doses that are too high. Conversely, for criterion 2, a low probability (less than 0.3) of observed toxicity greater than 0.2 (P ($\pi t < 0.2$) = 1- P ($\pi t > 0.2$) therefore criterion 2 corresponds to P $\pi t > 0.2$) <0.3) will increase the dose and thus allow the patient to benefit from a larger quantity of stem cells.

If none of the criteria is filled with patients will be included in the same starting dose, i.e. to 2.10^6MSC/kg.

An independent Committee will meet in order to validate the decision to stop the inclusions, decrease the dose or to increase it in the light of the results of sequential analysis.

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

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

12.8 Selection of populations

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

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

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

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

13.1.1 Strategy for site opening

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

13.1.2 Scope of site monitoring

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

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI 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

Paper CRF:

All information required by the protocol must be entered in the case report forms and an explanation must be given for all missing data. The data must be collected as and when they are obtained, and must be written clearly and legibly.

Any errors must be crossed out and the correct information entered next to the crossed-out data, together with the initials of the Investigator or authorised person who made the correction, the date and if necessary the reason for the correction.

13.4 Management of non-compliances

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

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

13.5 Audits/inspections

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

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

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

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

13.6 Principal Investigator's declaration of responsibility

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

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

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

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

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

The time of reflection of 24h will be given between receiving the information and being asked to sign the consent form.

The person's free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator, before the person is enrolled on the trial after validation of eligibity criteria (between M-3 and M0).

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

In addition, the investigator will specify in the research participant's medical file, the methods used for obtaining their consent or the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Special rule: If the person is unable to give his or her written consent, consent may be obtained, in descending order of priority, from a legal representative, family member or a close relative. These persons must have no connection whatsoever to the investigator or the sponsor

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

An exclusion period of 12months. will apply after the subject has finished this trial.

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial.

14.3 Compensation for subjects

No compensation will be awarded for this research.

14.4 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 (DRCI) in order to conduct the 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.

14.5 Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional s 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.

14.6 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.

14.7 Procedures relating to data protection regulations

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

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

On-the-view-to-public-to-use-the-public-to-public-to-data-based-personal data (cliniqual, biological, genetic data, etc.) will be implemented to analyze the results.
For this purpose, the medical data concerning you and data relating to your lifestyle, as well as, your ethnic background or data relating to your sex life if they are necessary for the research, will be transmitted to the Promoter or to persons or companies acting on his behalf, in France or abroad. These data will be identified by a registration number. These data may also, under conditions ensuring their confidentiality, be transmitted to French or foreign health authorities.

Medical data concerning the patient who can document a file with the competent authorities on the drug evaluated in this research, may be transmitted to an industrialist so that more patients can benefit from the results of the research. This transmission will be made under the conditions ensuring their confidentiality.

The patient's data may be used for further research or analysis complementary to this research in collaboration with private or public partners, in France or abroad, under conditions ensuring their confidentiality and the same level of protection as the European legislation.
The patient may withdraw consent at any time for further use of his or her data from the doctor who is following you for this research.
The computer file used for this research is implemented in accordance with the French regulations (Data Protection Act and modified) and European (the General Regulation on Data Protection -RGPD), the patient will have a right of access, rectification and opposition to the processing of privileged data used in this research. These rights are exercised by the doctor in charge of research who knows only the identity of the patient (identified on the front page of the patient information document).

If the patient decides to stop participating in the research, the data collected previously at this stop will be used in accordance with the regulations, and exclusively for the purposes of this research. Indeed, their erasure would be likely to compromise the validity of the results of the research. In this case, his data will not be used later or for any other search.

In the event of difficulties in the exercise of the rights of the patient, he / she may contact the AP-HP Data Protection Officer at the following address: protection.donnees.dsi@aphp.fr, who may in particular explain the remedies available to you at the CNIL.

The patient can also access directly or through a doctor of his choice to all of your medical data pursuant to the provisions of Article L 1111-7 of the Public Health Code.

14.8 Request for authorisation by the CNIL

As the processing of personal data for this trial is not governed by the MR 001 Reference Method, the sponsor must obtain approval from the CNIL.

14.9 Standard declaration to the CNIL

This is a single-centre trial conducted at just one hospital and therefore the AP-HP, as sponsor of the trial, has not made a standard declaration to the CNIL for this trial because this research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001).

14.10 Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

14.11 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.

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

Sources of funding for the trial is provided :

- A subvention in the case of Call for tenders « Subvention de recherche thérapie génique et cellulaire en néphrologie » funded by “Fondation du Rein et l’Association Française des Myopathies (AFM téléthon)”in collaboration with AIRG France entitled : “Subv.Thérapie génique FdR-AFM_AIRG 2014/FRM Dominique FARGE »

15.2 Insurance

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

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

16 PUBLICATION

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

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

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

16.3 Mention of the funder in the acknowledgements of the text

- “The study was funded by a grant from “Fondation du Rein et l’Association Française des Myopathies (AFM téléthon)”in collaboration with AIRG France, « Subvention de recherche thérapie génique et cellulaire en néphrologie » entitled : “Subv.Thérapie génique FdR-AFM_AIRG 2014/FRM Dominique FARGE »”
- The study was funded by a grant from DRCI, Assistance Publique – Hôpitaux de Paris

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

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18 APPENDIX - LIST OF ADDENDA

18.1 APPENDIX 1 - LIST OF CONTACTS

Type of location	Address of the study location	Title	Full name	Telephone / e-mail / Fax
Study Investigator Site	Internal Medicine : Auto-Immunes Diseases and Vascular Pathology Unit, Saint Louis Hospital, AP-HP, 1 avenue Claude Vellefaux. 75010 Paris.	**Professor, Coordinating investigator**	**Dominique FARGE-BANCEL**	Tel: 01 42 49 97 64. Fax 01 42 49 94 78. E-mail: dominique.farge-bancel-bancel@.aphp.fr
Cell Therapy Laboratories	Cell & Tissue Therapy, Royal Free London NHS FT & UCL	**Professor, Director of Cellular Therapeutics and RFH/UCL Cancer Biobank and responsible for CSM production at UCL**	**Mark LOWDELL**	Tel: 020 7830 2183 Email : m.lowdell@ucl.ac.uk
	Cell Therapy Unit (CTU), Saint Louis Hospital, AP-HP, 1 avenue Claude Vellefaux, 75010, Paris.	**Professor, Director of Cell Therapy Unit (CTU) at Saint Louis Hospital and responsible for CSM release from CTU to Investigator Site**	**Jérôme LARGHERO**	Tel 01 42 49 47 50. Fax 01 42 49 47 55. E-mail: jerome.larghero@aphp.fr
	Cell Therapy Unit (CTU), Saint Louis Hospital, AP-HP, 1 avenue Claude Vellefaux, 75010, Paris.	**Doctor, responsible for quality control for CSM release at CTU**	**Audrey CRAS**	Tel: 01 42 49 98 88. Fax 68/97 01 42 49 97 69. E-mail: audrey.cras@aphp.fr
Non Recruiting centers but only addressing patients to Pr Farge	**Lupus Reference Centers,** Internal Medicine Department, Civil Hospital, 1 place of the hospital, 67091 Strasbourg,	**Professor, Associate Investigator**	**Thierry MARTIN**	Tel. : 03 88 11 68 70 - Fax: 03 88 11 64 64 Email: thierry.martin@chru-strasbourg.fr
	Lupus Reference Centers, E3M Institut La Pitié Salpêtrière-Charles Foix - Pitié-Salpêtrière Hospital 47-83 boulevard de l'Hôpital, 75013 Paris	**Professor, Associate Investigator**	**Zahir AMOURA**	Tel.: 33 (0)1 42 17 80 01- Fax: 33 (0)1 42 17 78 34 Email: zahir.amoura@aphp.fr
	PURPAN Hospital, Internal Medicine, University Hospital of Toulouse, Place du Dr Joseph Baylac, 31300 Toulouse,	**Doctor, Associate Investigator**	***Grégory PUGNET***	Tel : 05 61 77 71 26 / 05 61 77 91 35 – Fax : 05 61 77 71 24 Email : pugnet.g@chu-toulouse.fr

18.2 APPENDIX 2 - SERIOUS ADVERSE EVENTS REPORT FORM

DECLARATION FORM OF SERIOUS ADVERSE EVENTS IN CELL THERAPY

To be keep in french language in request of DRCI for competent autority soumission

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Serious Adverse Event (SAE) form for a clinical trial conducted on an investigational medicinal product or a related product involving human subjects**	**SECTION FOR THE SPONSOR USE ONLY** **INTERNAL SAFETY REFERENCE:** GED Reference: REC-DTYP-0385

Please return this form (3 pages) completed and signed as soon as the investigator becomes aware of the SAE without delay to the Safety Department of the DRCI 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.

Initial report ☐ **Follow-up report** ☐ **Follow-up number** |__|__|

1. Clinical trial information

Acronym: MSC-SLE

Sponsor study number: P150302J

Risk: D

Date of report: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Date the investigator became aware of the SAE: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Full title of the clinical trial: Treatment of refractory systemic lupus erythematosus by injection of allogeneic mesenchymal stem cells derived from the umbilical cord

2. Clinical investigation center information

Center name: Saint Louis Hospital
City and address: 1 Avenue Claude Vellefaux, 75010 Paris, France
Department: Internal medicine Unit : Auto-Immune Diseases and Vascular Pathology, Center for cell therapy for autoimmune diseases within the Reference for autoimmune and rare systemic diseases

Investigator (last name/name): .....

Phone: ..... Fax: .....

3. Identification and medical history of the subject

Subject identification number: |__|__|__| - |__|__|__|__| - |__| -|__|
Center No. - Selection order No. - initial last name - initial name

Sex: ☐ M ☐ F

Age: |__|__|__| years

Weight: |__|__|__| kg
Height: |__|__|__| cm

Informed consent signature date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Please provide any medical, surgical or family history which may impact the assessment of the case (medical anonymized documentation to be attached as appropriate):

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

4. Investigational Medicinal Product (IMP) [Allogeneic mesenchymal stem cells derived from the umbilical cord] administered prior the occurring of the SAE *(cross out the box if the treatment has not started yet)*

IMP	Route (1)	Number of cells administered	Start date *(dd/mm/yyyy)*	Starting hour (if applicable)	Ongoing (2)	Ending hour
Allogeneic mesenchymal stem cells	.....	|__|__|,|__|__| X10^__ /Kg	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| h h |__|__| min	☐	|__|__| h h |__|__| min

5. Additional procedures or medical cares performed during the clinical trial *(cross out the box if no additional procedure has been performed)*	Date *(dd/mm/yyyy)*	Chronology	
		Before the SAE onset	After the SAE onset
Injection procedure (intervention)	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Biopsy	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

(1) Route of administration: PO=oral route; IM=intramuscular; IV=intravenous; SC=subcutaneous or other (specify) (2) Ongoing at the time of the SAE

SECTION FOR THE SPONSOR USE ONLY
INTERNAL SAFETY REFERENCE:

GED Reference: REC-DTYP-0385

Acronym: Erreur ! Source du renvoi introuvable. **MSC-SLE**

Patient identification number: |__|__|__| - |__|__|__|__| - |__| - |__|
Center No. - selection order No. - initial last name - initial first name

6. Concomitant Medication(s) at the time of the SAE, excluding those used to treat the SAE *(please fill the table below and the related annex on the concomitant medication(s) as appropriate. Cross out the box if not applicable.)*

⇨ **Annex attached to this form:** ☐ Yes ☐ No

Brand name (preferred) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Administration of the medicinal product date *(from dd/mm/yy to dd/mm/yy)*	Ongoing (2)	Indication	***Action undertaken*** *0: dosage remained unchanged 1: drug withdrawal 2: dosage reduction 3: dosage increasing 4: unknown*	***Causality of the SAE*** *0: not related to the drug 1: related to the drug 2: unknown*
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			

(1) Route of administration: PO=oral route; IM=intramuscular; IV=intravenous; SC=subcutaneous or other (specify) (2) Ongoing at the time of the SAE

7. Serious Adverse Event [SAE]

Diagnosis: ☐ Definitive ☐ Provisional

.....

.....

.....

Date first symptoms occurred: |__|__| |__|__| |_2_|_0_|__|__|

Describe the symptoms:

.....

Organ(s) affected:

.....

.....

.....

.....

.....

.....

Date of start of SAE:

|__|__| |__|__| |_2_|_0_|__|__|

dd mm yyyy

Onset time: |__||__| hh |__||__| min

☐ *missing data*

Time interval between the last treatment dose intake/absorption of the product or the date of the additional procedures or medical cares performed during the clinical trial and the start of the SAE:

|__||__| / |__||__| / |__||__|

dd hh min

Seriousness criteria:

☐ Hospitalization or prolongation of existing hospitalization:

from |__|__| |__|__| |_2_|_0_|__|__|

to |__|__| |__|__| |_2_|_0_|__|__| ☐ *ongoing*

☐ Death

☐ Life threatening

☐ Persistent or significant disability or incapacity

☐ Congenital anomaly/birth defect

☐ Other significant medical event, specify:

.....

.....

Severity :

CTCAE: ☐1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

The occurrence of the SAE led to:

☐ no action undertaken regarding the IMP

☐ IMP dosage reduction ☐ IMP dosage increasing

☐ definitive withdrawal of the IMP

☐ temporary withdrawal of the IMP, resumption date: |__|__| |__|__| |_2_|_0_|__|__|

☐ unknown

Recurrence of the SAE after resumption: ○ No ○ Yes, Date: |__|__| |__|__| |_2_|_0_|__|__|

○ Not applicable

Has any symptomatic measure been taken?

☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__| Specify: .....

Please specify if the SAE is the outcome of:

- A medication error? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- An overdose? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- A misuse? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- Other (specify): ..... ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|

Has the event been caused by an incident during the production, preparation, transformation, conservation, transportation, distribution or administration of the experimental product?

☐ No ☐ Yes Date of the incident: |__|__| |__|__| |_2_|_0_|__|__|

If so, please attach the Lot release certificate concerned and the biovigilance form if available.

The Biovigilance Local Correspondant (BLC) has been informed: ☐ No ☐ Yes

If so, please provide the contact information of the BLC: .....

Has any symptomatic measure been taken?

☐ No ☐ Yes Date : |__|__| |__|__| |_2_|_0_|__|__| Pleases specify: ……	

Subject identification number: |__|__|__| - |__|__|__|__| - |__| - |__|
Center No. - selection order No. - initial last name - initial name

SECTION FOR THE SPONSOR USE ONLY
INTERNAL SAFETY REFERENCE:

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

Outcome of the SAE

☐ **Death**
○ unrelated to the SAE
○ related to the SAE
Date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

☐ **Not yet recovered**, specify:
○ Stable condition ○ Improvement ○ Worsening

☐ **Resolved:**
○ without sequelae
○ with sequelae, specify the sequelae:
……
Date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy
|__|__| |__|__|
hh min

☐ **Unknown outcome**

8. Other etiology(ies) considered

☐ No ☐ Yes Specify: ……
……
……

9. Additional test(s) performed

☐ No ☐ Yes Please specify date, type and results: [please attach the anonymized reports where
……
……
……

10. According to the investigator, the SAE is (multiple choice allowed)

Related to the clinical trial:

☐ **Yes:** ☐ **to the Allogeneic mesenchymal stem cells:**
☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐ **Unlikely relationship**
☐ **to the additional procedures/care:**
☐ **Injection procedure (intervention)** ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐ **Unlikely relationship**
☐ **Biopsy** ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐ **Unlikely relationship**

☐ **No:** ☐ **to the disease progression (severe refractory systemic lupus erythematosus)**
☐ **to one (or more) concomitant medicinal product(s) administered, specify: ……**
☐ **to an intercurrent disease, specify: ……**
☐ **other, specify: ……**

Reporter:	**Investigator:**	Department stamp:
Name and function: Signature:	Name: Signature:	

18.3 APPENDIX 3- FICHE DE BIOVIGILANCE

Fiche BioVG-V1.3 ABM-2016

agence de la biomédecine

Fiche de BIOVIGILANCE
(Art. L1418-1 et R. 1211-33 9° du Code de la santé publique)
Recherche « MSC-LES » - Promotion AP-HP
Titre complet de la recherche : Traitement du lupus érythémateux systémique par injection de cellules souches mésenchymateuses allogéniques issues du cordon ombilical.

ORGANE ☐
TISSU ☐
CELLULES ☐
LAIT ☐

Direction générale médicale et scientifique
Pôle sécurité-qualité
Fax : 01 55 93 69 36
Mail : biovigilance@biomedecine.fr

BV

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

1. Signalant & déclarant

À remplir par le signalant	***À remplir par le correspondant local de biovigilance (CLB)***
Identité du signalant Nom : Prénom :	Identité du CLB Nom : Prénom :
Qualité :	Qualité :
Coordonnées du signalant Téléphone : Fax : E-mail : Adresse :	Coordonnées du CLB Téléphone : Fax : E-mail : Adresse :
	Date de la déclaration :
	Numéro de référence interne :
	☐Déclaration initiale ☐Suivi de déclaration (préciser le N° BV :……)

2. Produit(s) concerné(s)

Type de don ou de prélèvement	☐Allogénique ☐Autologue ☐Personnalisé ou intrafamilial
Nature du produit biologique et numéro d'identification ou nom du PTA, fabricant et numéro de lot	
Site de préparation* ou établissement de prélèvement* ou adresse du fabricant*	
Préciser le cas échéant si : ☐ Produit biologique importé Origine*/destination* de l'import*/export* :	☐Produit biologique exporté Date de l'import*/export* :

** Rayer les mentions inutiles*

3. Donneur et receveurs(s)impliqués *(ou potentiellement impliqués)*

Donneur		
Statut : ☐Vivant ☐SME[1] ☐DDAC-ACI[2] ☐DDAC-LAT[3] ☐PPM[4]		
N° identification :	Sexe : ☐ M ☐ F	Date de naissance
Date (ou période*) du (des) prélèvement(s) :	Etablissement de prélèvement :	
Receveur		
N° identification :	Sexe : ☐ M ☐ F	Date de naissance
Date (ou période*) de greffe/administration :	Etablissement de greffe/administration :	

Autres receveurs : ☐ oui (préciser ci-dessous dans le tableau ☐ non				
N° identification				
Nature produit biologique**				
Date (ou période*) de greffe/administration				
Etablissement de greffe/administration				

[1] SME : sujet en état de mort encéphalique et à cœur battant
[2] DDAC-ACI : donneur décédé après arrêt circulatoire suite à un arrêt cardiaque inopiné
[3] DDAC-LAT : donneur décédé après arrêt circulatoire suite à la limitation ou l'arrêt des thérapeutiques
[4] PPM : donneur de tissus prélevé en post-mortem à la morgue

agence de la biomédecine

Fiche de BIOVIGILANCE
(Art. L1418-1 et R. 1211-33 9° du Code de la santé publique)
Recherche « MSC-LES » - Promotion AP-HP
Titre complet de la recherche : Traitement du lupus érythémateux systémique par injection de cellules souches mésenchymateuses allogéniques issues du cordon ombilical.

ORGANE ☐
TISSU ☐
CELLULES ☐
LAIT ☐

4. Description de l'incident et/ou de l'effet indésirable

Le cas échéant joindre une description plus complète sur papier libre. Préciser le nombre de pages jointes (et rappeler le nom de l'émetteur sur chaque page) : ☐

Date *(☐ survenue ou ☐ mise en évidence)* :

☐de l'incident

☐ de l'effet indésirable (donneur* ou receveur*)

** Rayer les mentions inutiles*

Intensité de l'effet indésirable :

Initiale ☐1 ☐2 ☐3 ☐4 ☐5

Finale ☐1 ☐2 ☐3 ☐4 ☐5

1-Négligeable : Manifestations cliniques ou biologiques ne nécessitant aucune prise en charge ou traitement médical.
2-Modérée : Manifestations cliniques ou biologiques sans menace vitale à court ou long terme et ne nécessitant pas d'hospitalisation.
3-Sévère : Manifestations cliniques ou biologiques entraînant une invalidité ou une incapacité, ou provoquant, prolongeant ou compliquant une hospitalisation ou tout autre état morbide, ou nécessitant une intervention médicale ou chirurgicale pour éviter un dommage permanent ou la défaillance d'une fonction corporelle.
A noter : les infections sévères susceptibles d'avoir été transmises par le produit biologique ou les activités de prélèvement ou de greffe/administration doivent systématiquement être déclarées et ceci à un niveau de gravité supérieur ou égal à 3.
4-Majeure : Menace vitale immédiate.
5-Décès.

Description :

Enquête : ☐en cours ☐non réalisé* ☐non réalisable*

☐ terminé - date de clôture :

Préciser l'analyse des causes (et leur conclusion pour les enquêtes terminées)

*****si l'enquête n'a pas été réalisée, dire précisément pour quelles raisons cette décision a été prise.

Imputabilité (lien entre le produit ou l'activité de prélèvement ou de greffe/administration et l'effet indésirable en début et en fin d'enquête)

Initiale : ☐1- Exclue/improbable ☐2- Possible ☐3- Vraisemblable/probable ☐4- Certaine ☐5- non évaluable

Finale : ☐1- Exclue/improbable ☐2- Possible ☐3- Vraisemblable/probable ☐4- Certaine ☐5- non évaluable

5. Evaluation locale de la criticité et des mesures prises

Probabilité de récurrence de l'effet indésirable ou de l'incident (probabilité pour que l'évènement se reproduise au vu des contrôles mis en place) :

☐ R1- rare ☐R2- peu probable ☐R3- possible ☐R4- vraisemblable ☐R5- pratiquement certaine ☐5- non évaluable

Conséquences potentielles de l'effet indésirable ou de l'incident sur les patients ou sur le stock

☐ C1 ☐C2 ☐C3 ☐C4 ☐C5 non évaluable

1-**Négligeables** (absence de manifestations cliniques et/ou biologiques ou de conséquence pour le stock de produits).
2-**Modérées** (manifestations cliniques et/ou biologiques modérées ne nécessitant pas obligatoirement une intervention médicale ou un traitement correcteur ou retard de quelques greffes ou administrations).
3-**Importantes** (invalidité ou incapacité permanente, intervention médicale et traitement correcteur ou annulation ou retard de plusieurs greffes ou administrations).
4-**Majeures** (menace vitale pour le ou les patients ou nombre significatif de greffes ou d'administrations annulées nécessitant, le cas échéant, le recours à des produits importés).
5-***Alarmantes*** **(décès du ou des patients ou annulation de toutes greffes ou administrations).**

Description des mesures mises en œuvre localement pour diminuer la criticité (RxC) :

6. Diffusion de l'information

Autre(s) correspondant(s) de biovigilance informé(s) : ☐Non ☐Oui (préciser lieu et date) :

Date de l'information de l'ABM (SRA et/ou CLB de l'ABM) :

Autre(s) vigilance(s) informée(s) : ☐Non ☐Oui (préciser) :

Autre(s) équipes informée(s) : ☐Non ☐Oui (préciser lieu et date) :

Date et signature du correspondant local de biovigilance

18.4 APPENDIX 4- FORMULAIRE DE NOTIFICATION DE GROSSESSE

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Follow-up form for reporting a pregnancy occurring in a clinical trial**	SECTION FOR THE SPONSOR USE ONLY INTERNAL SAFETY REFERENCE: GED Reference: REC-DTYP-0288

This form must be duly completed (3 pages), signed and sent immediately to the Safety Department (DRCI) 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.

1. Clinical trial identification

Acronym: MSC-SLE
Sponsor study number: **P150302J**

Initial report ☐ **Follow-up report** ☐ **Follow-up N°** |__|__|

Date of report: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Date the investigator became aware of pregnancy: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Full title of the clinical trial: Treatment of refractory systemic lupus erythematosus by injection of allogeneic mesenchymal stem cells derived from the umbilical cord

2. Identification of the clinical investigation centre

Center name: Saint Louis Hospital

City and adress: 1 Avenue Claude Vellefaux, 75010 Paris
Country: France

Department: Internal medicine Unit : Auto-Immune Diseases and Vascular Pathology, Center for cell therapy for autoimmune diseases within the Reference for autoimmune and rare systemic diseases

Investigator (last name/name): .....

Phone number: Fax:

3. Identification of subject presenting pregnancy

Subject reference: |__|__|__| - |__|__|__|__| - |__| - |__|
centre n° - selection order n° - surname initial - first name initial

Age: |___|___|__|years
Inclusion date: |__|__| |__|__| |_2_|_0_|__|__|
Date of last menstrual period: |__|__| |__|__| |_2_|_0_|__|__|
And/or pregnancy start date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Specific case of exposure involving the father: ☐ No ☐ Yes

Subject reference: |__|__|__| - |__|__|__|__| - |__| - |__|
centre n° - selection order n° - surname Initial - first name initial

Date of birth: |__|__| |__|__| |___|___|__|__|
Inclusion date: |__|__| |__|__| |_2_|_0_|__|__|

Exposures during pregnancy:

Tobacco:	☐ no	☐ yes (specify number) :	☐ stopped on (specify date):	☐ ongoing
Alcohol:	☐ no	☐ yes (specify OH units) :	☐ stopped on (specify date):	☐ ongoing
Drug:	☐ no	☐ yes (specify substance) :	☐ stopped on (specify date):	☐ ongoing

Other substances (specify):

4. Maternal history

Medical:

Surgical:

Obstetrical: |__|__| gravida |__|__| para
Specify any miscarriages, ectopic pregnancies, abortions, medical termination of pregnancy, stillbirths, congenital malformations (birth defects), non-malformative congenital/neonatal pathologies, etc. *(number, date and nature/reason, if applicable).*

5. Investigational Medicinal Product (IMP) [Allogeneic mesenchymal stem cells derived from the umbilical cord] administered prior the occurring of the SAE ***(cross out the box if the treatment has not started yet)***

IMP	Route (1)	Number of cells administered	Start date *(dd/mm/yyyy)*	Starting hour (if applicable)	Ongoing (2)	Ending hour
Allogeneic mesenchymal stem cells	.....	|__|__|,|__|__| X10^__ /Kg	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| h h |__|__| min	☐	|__|__| h h |__|__| min

6. Additional procedures or medical cares performed during the clinical trial *(cross out the box if no additional procedure has been performed)*	Date *(dd/mm/yyyy)*	Chronology	
		Before the SAE onset	After the SAE onset
Injection procedure (intervention)	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Biopsy	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

7. Concomitant medication(s)

Commercial name (preferred) or International Non-proprietary Name	Date of first administration	Date of last administration Or ongoing	Route of administration(1)	Dose / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ Ongoing		

(1) Route of administration: O=orally; IM=Intramuscular; IV=intravenous; SC=subcutaneous or other (please specify)

8. Pregnancy follow-up

☐ Ultrasounds. Specify date(s) and results:

☐ Other exams. Specify date(s) and results *(attach reports)*:

9. Current pregnancy ☐ (fax another completed form on outcome of pregnancy)
or Outcome of pregnancy ☐ (complete the box below)

Date: |__|__| |__|__| |_2_|_0_|__|__| Term: |__|__| WA |__|__| D

☐ Miscarriage
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Ectopic pregnancy
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Abortion → Reason:
→ Anatomopathological exams available: ☐ No ☐ Yes, please specify result:

☐ Delivery: ☐ Spontaneous ☐ Induced ☐ Vaginal ☐ Caesarean

Multiple birth: ☐ No ☐ Yes, please specify number:
Foetal distress: ☐ No ☐ Yes, please specify:
Stillbirth: ☐ No ☐ Yes, please specify:
Placenta normal: ☐ Yes ☐ No, please specify:
Amniotic fluid: ☐ Clear ☐ Other, please specify:
Anaesthesia: ☐ General ☐ Epidural ☐ Spinal anaesthesia ☐ None

10. Newborn information (for multiple births, please complete sections 1, 2, 3, 9 and 10 on a different form and send by fax)

Sex: ☐ Male ☐ Female

Weight: |__|__|__|__| grams Height: |__|__|__| cm Head circumference: |__|__|__| cm

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

Congenital malformation(s): ☐ No ☐ Yes, please specify:

Non-malformative(s) congenial(s)/neonatal(s) pathology(ies): ☐ No ☐ Yes, please specify:		
Did the newborn receive any specific treatment at birth: ☐ No ☐ Yes, please specify:		
Reporter	**Investigator**	Department stamp:
Name and function:	Name:	
Signature:	Signature:	

18.5 APPENDIX 5 - TECHNICAL DATA FORM FOR PHENOTYPE, CYTOKINES, CROSSMATCH, AND BANKING IN SITI LABORATORY (CHU DE RENNES)

Samples will be routed in such a way that they arrive no later than Friday before 1: 00 pm to SITI laboratory (CHU de Rennes, Pr K. Tartes)

Tubes taken:
6 gel-free lithium heparin tubes of 4ml : phenotyping, cytokines (plasma) and back-up cells
1 dry tube of 7ml: Serum isolation for cytokines and crossmatch
1 RNA Paxgene tube of 2,5ml: RNA banking

Follow-up :

- Before injection of MSCs: all tubes described above
- 1 month after injection of MSC: all tubes described above
- 1 sample at 3 months after injection of MSC: all tubes described above
- 1 sample at 6 months after injection of MSC: only 6-gel-free lithium heparin tubes
- 1 sample at 12 months after injection of MSC: only 6-gel-free lithium heparin tubes

Objectives:

Analysis in the circulating blood of the various subpopulations of cells involved in the immune response, for monitoring an immunomodulation mediated MSCs.

- Tube T B NK : 3/16+56/19

- **LYMPHOCYTE PHENOTYPING OF PATIENT**

This is a phenotyping focused on transplant issues in a context of autoimmunity. It involves assessing:

Monocytes subpopulations frequency
CCR2, CD14, CD11b, CD335, CD19, CD163, HLA DR, CD64, CD45, CD16, CD3

Dendritic cells (DC) plasmacytoid and myeloid major subpopulations of DC circulating, using specific markers
CD172a/b (SIRPa/b), CD141, CD11b, CD274 (PDL-1), CD123, CD86, HLA DR, CD1c, CD11c, CD4, CD56, CD19, CD14, CD16, CD3

Lymphocytes :

- B Lymphocytes :
  - Monitoring of the different lymphocyte subpopulations B CD10, CD5, IgM, CD24, CD27, IgD, CD38, CD22, CD19, CD3, CD14, CD138, CD20
- T Lymphocytes :
  - status T cell activation and
  - subpopulations : HLA DR, CD49b, CD45RA, CD31, CD223 (LAG3), CD69, CD197 (CCR7), CD3, CD4, CD8
- - Th Lymphocytes:
  subpopulations Tracking Th1, Th2 and Th17 with the expression of certain chemokine receptors : CCR4 , CD45RA, HLA DR, CXCR3, CCR6, CD161, CD279 (PD1), CD185 (CXCR5), CD3, CD4, CD25
  -
- - Treg lymphocytes:
  - Frequency of Treg cells and thymic emigrants:

CD127, HLA DR, CD39, CD45RA, CD25, Ki67, FOXP3, CD197 (CCR7), CD3, CD4, CD8

- Lymphocytes NK
  - Frequency of NK cells:CD45/CD3/CD14/CD16/CD56/CD57/NKG2C/PanKIR2D
  - CD314 (NKG2D), CD56, CD45RO, CD19, CD335 (NKP46), CD69, CD57, CD336 (NKP44), CD45, CD16, CD4, CD3.

- **STORAGE OF SERUM, PBMC and RNA**
  - PBMC: at 2-5.10^6 cells per cryotube in SVF-10%DMSO in liquid nitrogen in the SITI for further subsequent phenotyping
  - RNA: paxgene tubes stored at -20°c until RNA extraction. RNA stored at -80°c for transcriptomic and/or T cell repertoire Research
  - Serum: stored in microtubes at -80°c until their use for cross-match assay and/or quantification of cytokine by ELISA or Luminex
  - Plasma: stored in microtubes at -80°c until their use for cytokine tittering by ELISA or Luminex

- **QUANTIFICATION OF CYTOKINES**
  Cytokines of interest will be quantified in the sera or plasma using ELISA or Luminex technologies.

- **CROSS-MATCH**
  The cytotoxicity of the recipient's sera against injected MSCs will be studied.

18.6 APPENDIX 6 - SLE DEFINITION CRITERIA

American College of Rheumatology Criteria for Systemic Lupus Erythematosus

Criteria	Description	Present
Malar rash	• Fixed malar erythema, flat or raised	
Discoid rash	• Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	
Photosensitivity	• Skin rash as an unusual reaction to sunlight, by patient history or physician observation	
Oral ulcers	• Oral and nasopharyngeal ulcers, usually painless, observed by physician	
Arthritis	• Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness swelling, or effusion	
Serositis	• Pleuritis (convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion) • Pericarditis (documented by ECG or rub or evidence of pericardial effusion)	
Renal disorder	• Persistent proteinuria >0.5 g/d or >3+ if quantification not performed • Cellular casts, may be red cell, hemoglobin, granular, tubular, or mixed	
Neurologic disorder	• Seizures - in the absence of offending drugs or known metabolic derangements: e.g., uremia, ketoacidosis, or electrolyte imbalance • Psychosis - in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance	
Hematologic disorder	• Hemolytic anemia – with reticulocytosis • Leukopenia (<4000/mm^3 total on 2 or more occasions). • Lymphopenia (<1500/mm^3 on 2 or more occasions) • Thrombocytopenia (<100,000/mm^3 in the absence of offending drugs)	
Immunologic disorder	• Anti-dsDNA: antibody to native DNA in abnormal titer • Anti-Sm: presence of antibody to Sm nuclear antigen • Positive finding of antiphospholipid antibodies based on 1) An abnormal serum level of IgG or IgM anticardiolipin antibodies 2) A positive test result for lupus anticoagulant using a standard method, or 3) A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	
Antinuclear antibodies	• An abnormal titer of ANA by immunoflorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug induced lupus" syndrome	

18.7 APPENDIX 7 - BILAG SCORE

BILAG (British Isles Lupus Assessment Group index)

Patient_____ Date_____

All features must be attributable to SLE and refer the last four weeks compared with the prior visit's disease activity.
Indicate and score which features are present: 0 = Not Present, 1 = Improving, 2 = Same, 3 = Worse, 4 = New or Recurrence.

General – MUST BE SLE RELATED		**Neurological - MUST BE SLE RELATED**	
1. Pyrexia (documented)	0 1 2 3 4	24. Deteriorating level of consciousness	0 1 2 3 4
2. Weight Loss – unintentional >5%	0 1 2 3 4	25. Acute psychosis, delirium, confusion	0 1 2 3 4
3. Lymphadenopathy/Splenomegaly	0 1 2 3 4	26. Seizures	0 1 2 3 4
4. Fatigue/Malaise/Lethargy	0 1 2 3 4	27. Stroke or stroke syndrome	0 1 2 3 4
5. Anorexia/nausea/vomiting	0 1 2 3 4	28. Aseptic Meningitis	0 1 2 3 4
Mucocutaneous - MUST BE SLE RELATED		29. Mononeuritis multiplex	0 1 2 3 4
6. Maculopapular eruption – severe, active, (bullous)	0 1 2 3 4	30. Ascending or transverse myelitis	0 1 2 3 4
7. Maculopapular eruption – mild	0 1 2 3 4	31. Peripheral or cranial neuropathy	0 1 2 3 4
8. Active discoid lesions – generalized / extensive	0 1 2 3 4	32. Disc swelling/cytoid bodies	0 1 2 3 4
9. Active discoid lesions – localized including lupus profundus	0 1 2 3 4	33. Chorea	0 1 2 3 4
10. Alopecia (severe, active)	0 1 2 3 4	34. Cerebellar ataxia	0 1 2 3 4
11. Alopecia (mild)	0 1 2 3 4	35. Headache severe, unremitting	0 1 2 3 4
12. Panniculitis (severe)	0 1 2 3 4	36. Organic depressive illness	0 1 2 3 4
13. Angioedema	0 1 2 3 4	37. Organic brain syndrome including	0 1 2 3 4
14. Extensive mucosal ulceration	0 1 2 3 4	Pseudotumor cerebri	0 1 2 3 4
15. Small mucosal ulcers	0 1 2 3 4	38. Episodic migranous headaches	0 1 2 3 4
16. Malar erythema	0 1 2 3 4	**Musculoskeletal - MUST BE SLE RELATED**	
17. Subcutaneous nodules	0 1 2 3 4	39. Definite myositis (Bohan & Peter)	0 1 2 3 4
18. Perniotic Skin Lesions	0 1 2 3 4	40. Severe Polyarthritis with loss of function	0 1 2 3 4
19. Periungal erythema	0 1 2 3 4	41. Arthritis	0 1 2 3 4
20. Swollen fingers	☐Yes ☐No	42. Tendonitis	0 1 2 3 4
21. Sclerodactyly	☐Yes ☐No	43. Mild chronic myositis	0 1 2 3 4
		44. Athralgia	0 1 2 3 4
22. Calcinosis	☐Yes ☐No	45. Myalgia	0 1 2 3 4
23. Telangiectasia	☐Yes ☐No	46. Tendon contractures and fixed deformity	☐Yes ☐No
		47. Aseptic necrosis	☐Yes ☐No

Cardiovascular & Respiratory - MUST BE SLE RELATED		Renal - MUST BE SLE RELATED		(√) if SLE Related
48. Pleuropericardial pain	0 1 2 3 4	68. Systolic Blood Pressure (Enter value)	_____mm-Hg	☐
49. Dyspnea	0 1 2 3 4	69. Diastolic Blood Pressure (Enter value)	_____mm-Hg	☐
50. Cardiac Failure	0 1 2 3 4	70. Accelerated Hypertension	☐Yes ☐No	☐
51. Friction Rub	0 1 2 3 4	71. Urine dipstick (Enter value) (- = 0) (+ = 1) (++ = 2) (+++ = 3)		☐
52. Effusion (pericardial or pleural)	0 1 2 3 4	72. Urinary protein (Record a or b) a. 24 hr urinary protein b. Urine protein-creatine ratio	a _____ g b _____mm/mmol	☐
53. Mild or intermittent chest pain	0 1 2 3 4	73. Proteinuria (Record a or b) a. Newly documented proteinuria of > 1g/24 hours b. Newly documented protein-creatine ratio of >100mg/mmol	a. ☐Yes ☐No b. ☐Yes ☐No	
54. Progressive CXR changes – lung fields *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle: No / Not Done	74. Nephrotic Syndrome	☐Yes ☐No	☐
55. Progressive CXR changes – heart size *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle No / Not Done	75. Creatinine (serum) (Enter value)	_____mg/dl	☐
56. ECG evidence of pericarditis or Myocarditis *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle No / Not Done	76. Creatinine clearance/GFR (Enter value)	_____ml/min	☐
57. Cardiac dysrhythmias including tachycardia >100 in the absence of fever *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle No / Not Done	77. Active urinary sediment	☐Yes ☐No	☐
58. Pulmonary function fall by 20% *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle No / Not Done	78. Histological evidence of active Nephritis - within 3 months	☐Yes ☐No	
59. Cytohistological evidence of inflammatory lung disease *If Not Done,√ NO on EDC BILAG	☐Yes OR Circle No / Not Done	86. Evidence of circulating anticoagulant	☐Yes ☐No	
Vascular - MUST BE SLE RELATED		**Hematology - MUST BE SLE RELATED**		
60. Major cutaneous vasculitis incl. ulcers	0 1 2 3 4	79. Hemoglobin (g/dl) (Enter value)	_____g/dl	☐
61. Major abdominal crisis due to vasculitis	0 1 2 3 4	80. Total white cell count (x 10^9/L) (Enter value)	_____x 10^9/L	☐
62. Recurrent thromboembolism excluding strokes	0 1 2 3 4	81. Neutrophils (x 10^9/L) (Enter value)	_____ x 10^9/L	☐
63. Raynaud's	0 1 2 3 4	82. Lymphocytes (x 10^9/L) (Enter value)	_____ x 10^9/L	☐
64. Livido reticularis	0 1 2 3 4	83. Platelets (x 10^9/L) (Enter value)	_____ x 10^9/L	☐
65. Superficial phlebitis	0 1 2 3 4	84. Evidence of active hemolysis	☐Yes ☐No	☐
66. Minor cutaneous vasculitis (nailfold vascultitis, digital vasculitis)	0 1 2 3 4	85. Coombs test positive	☐Yes ☐No	
67. Thromboembolism (excl. stroke) (first episode)	☐Yes ☐No	86. Evidence of circulating anticoagulant	☐Yes ☐No	

18.8 APPENDIX 8 - SELENA SLEDAI SCORE

Interest

Provides an assessment of the activity of SLE. The weight assigned to each variable was determined by multiple regression analysis. The events described are taken into account if they are present on the day of consultation or in the previous 10 days.

Method

Checking the presence or absence of 24 variables

Results

They range from 0-105

Patient Name: _____ Evaluation date: _____

Co-investigator / _____

(Note the value in the "SLEDAI score" column if the described signs are present at the time of the assessment or in the previous 10 days.)

SLEDAI: DATA COLLECTION SHEET

Date of Visit: _____ Patient's No: _____

SLEDAI Score Descriptor Definition

8 _____	Seizure	Recent onset. Exclude metabolic, infectious, or drug causes.
8 _____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associa- tions, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8 _____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8 _____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8 _____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8 _____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8 _____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8 _____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angio- gram proof of vasculitis.
4 _____	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4 _____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electro- myogram changes or a biopsy showing myositis.
4 _____	Urinary casts	Heme-granular or red blood cell casts.
4 _____	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other cause.

4 _____	Proteinuria	> 0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4 _____	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2 _____	New rash	New onset or recurrence of inflammatory type rash.
2 _____	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2 _____	Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations.
2 _____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2 _____	Pericarditis.	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2 _____	Low complement.	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2 _____	Increased DNA binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1 _____	Fever > 38°C.	Exclude infectious cause.
1 _____	Thrombocytopenia	< 100,000 platelets/mm3.
1 _____	Leukopenia	< 3,000 white blood cells/mm3. Exclude drug causes.

TOTAL **SLEDAI** SCORE _____

18.9 APPENDIX 9 - SRI SYSTEMIC LUPUS ERYTHEMATOSUS RESPONDER INDEX

SRI is a composite score that incorporates a modification of SLEDAI, estrogen security in Lupus: national assessment test (SELENA SLEDAI-), BILAG activity index and the PGA.

18.10 APPENDIX 10 - SLICC-ACR & Charlson Comorbidity Index

- **SLICC / ACR DAMAGE INDEX**

Chronic lesions of lupus patient may be due to lupus or any other cause, such as atherosclerosis, hypercoagulability, hypertension, SLE medications or other comorbidities. This index summarizes all the damage whatsoever in either the mechanism. The injury is defined as an irreversible change, unrelated to active inflammation, appeared after diagnosis of lupus, authenticated by ***clinical assessment and present for at least 6 months.***

SLICC/ACR DAMAGE INDEX FOR SLE

Centre: **Patient ID:** **Date of Assessment:**

Damage (non-reversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

OCULAR		
Any cataract ever (documented by ophthalmoscopy)	**1**	
Retinal change ***OR*** Optic atrophy (documented by ophthalmoscopy)	**1**	
(2) **NEUROPSYCHIATRIC**		
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) ***OR*** Major psychosis	**1**	
Seizures requiring therapy for 6 months	**1**	
	1	**2**
Cerebrovascular accident ever or surgical resection (for non-malignant causes) (score 2 if >1)	**1**	
Cranial or peripheral neuropathy (excluding optic)	**1**	
Transverse myelitis		
RENAL		
Estimated/Measured GFR < 50%	**1**	
Proteinuria ≥ 3.5g/24 hours	**1**	
OR		
End-stage renal failure (regardless of dialysis or transplantation)	**3**	
PULMONARY		
Pulmonary hypertension (right ventricular prominence or loud P2)	**1**	
Pulmonary fibrosis (physical & radiograph)	**1**	
Shrinking lung (radiograph)	**1**	
Pleural fibrosis (radiograph)	**1**	

Pulmonary infarction (radiograph) or resection (for non-malignant causes)	**1**	
CARDIOVASCULAR		
Angina ***OR*** Coronary artery bypass	**1**	
Myocardial infarction ever (score 2 if > 1)	**1**	**2**
Cardiomyopathy (ventricular dysfunction)	**1**	
Valvular disease (diastolic, murmur, or systolic murmur > 3/6)	**1**	
Pericarditis for 6 months ***OR*** Pericardiectomy	**1**	
PERIPHERAL VASCULAR		
Claudication for 6 months	**1**	
Minor tissue loss (pulp space)	**1**	
Significant tissue loss (eg loss of digit or limb) (score 2 if > 1)	**1**	**2**
Venous thrombosis with swelling ulceration ***OR*** Venous stasis (clinical)	**1**	
GASTROINTESTINAL		
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder for any cause (score 2 if > 1)	**1**	**2**
Mesenteric insufficiency	**1**	
Chronic peritonitis	**1**	
Stricture OR Upper gastrointestinal surgery	**1**	
Pancreatic insufficiency requiring enzyme replacement or with pseudocyst	**1**	
MUSCULOSKELETAL		
Muscle atrophy or weakness	**1**	
Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis)	**1**	
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	**1**	**2**
Avascular necrosis (imaging) (score 2 if > 1)	**1**	
Osteomyelitis (supported by culture evidence)	**1**	
Tendon rupture	**1**	
SKIN		
Scarring chronic alopecia	**1**	
Extensive scarring or panniculum other than scalp and pulp space	**1**	
Skin ulceration for > 6 months (excluding thrombosis)	**1**	

PREMATURE GONADAL FAILURE (secondary amenorrhoea before age 40)	**1**	
DIABETES MELLITUS (regardless of treatment)	**1**	
MALIGNANCY (exclude dysplasia) (score 2 if > 1 site)	**1**	**2**

For the Charlson Comorbidity Index : https://www.mdcalc.com/charlson-comorbidity-index-cci

18.11 APPENDIX 11 - SF-36v2 SCORE

HOW TO ANSWER: The following questions are about your health, as you feel. This information will allow us to better know how you feel in your daily life.
Please answer all questions by circling the number corresponding to the selected answer, as indicated. If you are not sure how to answer, choose the closest answer to your situation.

1. Overall, do you think your health is:

Circle the answer of your choice

-Excellent 1
-Very Good 2
-Good 3
-Poor 4
-Bad 5

2. Compared to last year at this time, how do you find your health now?

Circle the answer of your choice

- Much better than last year 1
- Rather Best 2
- A About the same 3
- Rather Less good 4
- Much worse 5

3. Here is a list of activities that you may have to make in your life everyday. For each of them whether you're limited (e) because of your current health status.

Circle the answer of your choice

Liste d'activités	Yes, Very limited	Yes, a few limited	No, not at all limited
a. **Important physical efforts** such as running, lifting heavy objects, doing sports	1	2	3
b. **Moderate physical activity** such as moving a table, vacuuming, playing boules	1	2	3
c. Lifting and carrying groceries	1	2	3
d. Climb **several floors** by stairs	1	2	3
e. Up **one floor** by the stairs	1	2	3
f. Lean forward, kneel, crouch	1	2	3
g. Walk more than **one kilometer** on foot	1	2	3
h. Walk **several hundred meters**	1	2	3
i. Walking **a hundred meters**	1	2	3
j. Take a bath, shower or dressing	1	2	3

4. Over the past 4 weeks, and because of your physical statement,

Circle the answer of your choice

	YES	NO

a. Did you reduce the **time spent** on your work or your usual activities	1	2
b. Do you accomplish **less than** you would have wished	1	2
c. Did you have to stop doing **certain** things	1	2
d. Have you had **difficulty** doing your work or other activities (for example, it asked you extra effort)	1	2

5. Over the past 4 weeks, and because of your emotional state (as you feel sad, nervous or depressed

Circle the answer of your choice

	YES	NO
a. Did you reduce the **time spent** on your work or your usua activities)	1	2
b. Do you **accomplish less than** you would have liked	1	2
c. Did you have difficulty doing what you had to do with **as much care and attention** as usual	1	2

6. Over the past 4 weeks how your state of health, physical or emotional, he embarrassed you (e) in your social life and your relationships with others, your family, your friends, your knowledge?

Circle the answer of your choice

-Not at all.....1
-A little.....2
-Moderately 3
-Many.....4
-Very Much 5

7. Over the past 4 weeks, what was the intensity of your physical pain?

Circle the answer of your choice

-Null 1
-Very low..... 2
-Low..... 3
-Average 4
-Large 5
-Very great..... 6

8. Over the past 4 weeks, how your physical pain Have you limited (e) in your work or household activities?

Circle the answer of your choice

-Not at all.....1
-A little.....2
-Average 3
-Many.....4
-Very Much 5

9. The following questions relate to how you felt during the last 4 weeks. For each question, please give the answer that seems most appropriate. Over the past 4 weeks, were there have been times where :

Circle the answer of your choice

	In permanence	Very often	often	Sometimes	Rarely	Never
a. You felt (e) Dynamic?	1	2	3	4	5	6
b. You felt very nervous?	1	2	3	4	5	6
c. You felt so discouraged that nothing could cheer you up?	1	2	3	4	5	6
d. You felt calm and relaxed?	1	2	3	4	5	6
e. You felt overflowing energy?	1	2	3	4	5	6
f. You felt sad and depressed?	1	2	3	4	5	6
g. You felt exhausted?	1	2	3	4	5	6
h. You felt happy?	1	2	3	4	5	6
i. You felt tired?	1	2	3	4	5	6

10. Over the last 4 weeks ago there were times when your health status, physical or emotional, has embarrassed you (e) in your social life and your relationships with others, your family, your friends, knowledge?

Circle the answer of your choice

-In permanence..... 1
-Much of the time..... 2
-From time to time..... 3
-Rarely..... 4
-Never..... 5

11. Indicate for each of the following statements, to what extent they are true or false in your case:

Circle the answer of your choice

	Totaly true	Rather true	I do not know	Rather false	Totaly false
a. I fall ill more easily than others	1	2	3	4	5
b. I am as good as anyone	1	2	3	4	5
c. I expect my health deteriorates	1	2	3	4	5
d. I am in excellent health	1	2	3	4	5

PLEASE CHECK THAT YOU HAVE PROVIDED A RESPONSE FOR EACH QUESTION.
THANK YOU FOR YOUR COLLABORATION

Questionnaire de santé SF36

Date |__|__| |__|__| |__|__|

Comment répondre

Les questions qui suivent portent sur votre santé, telle que vous la ressentez. Ces informations nous permettront de mieux savoir comment vous vous sentez dans votre vie de tous les jours.

Veuillez répondre à toutes les questions en entourant le chiffre correspondant à la réponse choisie, comme il est indiqué. Si vous ne savez pas très bien comment répondre, choisissez la réponse la plus proche de votre situation.

Identification

1. Dans l'ensemble, pensez-vous que votre santé est :
(entourez la réponse de votre choix)

Excellente	1
Très bonne	2
Bonne	3
Médiocre	4
Mauvaise	5

2. Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé en ce moment ? *(entourez la réponse de votre choix)*

Bien meilleur que l'an dernier	1
Plutôt meilleur	2
À peu près pareil	3
Plutôt moins bon	4
Beaucoup moins bon	5

3. Au cours de ces 4 dernières semaines, et en raison de votre état physique
(entourez la réponse de votre choix, une par ligne)

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles ?	1	2
b. Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
c. Avez-vous dû arrêter de faire certaines choses ?	1	2
d. Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire)	1	2

4. Au cours de ces 4 dernières semaines, et en raison de votre état émotionnel (comme vous sentir triste, nerveux(se) ou déprimé(e))
(entourez la réponse de votre choix, une par ligne)

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	1	2
b. avez-vous accompli moins de choses que vous auriez souhaité	1	2
c. avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention que d'habitude	1	2

5. Au cours de ces 4 dernières semaines dans quelle mesure votre état de santé, physique ou émotionnel, vous a-t-il gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances
(entourez la réponse de votre choix)

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

6. Au cours de ces 4 dernières semaines, quelle a été l'intensité de vos douleurs (physiques) ?
(entourez la réponse de votre choix)

Nulle	1
Très faible	2
Faible	3
Moyenne	4
Grande	5
Très grande	6

7. Au cours de ces 4 dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques?
(entourez la réponse de votre choix)

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

8. Au cours de ces 4 dernières semaines. y a-t-il eu des moments où votre état de santé. physique ou émotionnel, vous a gêné(e) dans votre vie et vos relations avec les autres, votre famille, vos amis, vos connaissances ?
(entourez la réponse de votre choix)

En permanence	1
Une bonne partie du temps	2
De temps en temps	3
Rarement	4
Jamais	5

9. Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours.
Pour chacune d'entre elles indiquez si vous êtes limité(e) en raison de votre état de santé actuel.
(entourez la réponse de votre choix, une par ligne)

Liste d'activités	Oui, beaucoup limité(e)	Oui, un peu limité(e)	Non, pas du tout limité(e)
a. Efforts physiques importants tels que courir, soulever un objet lourd, faire du sport	1	2	3
b. Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	1	2	3
c. Soulever et porter les courses	1	2	3
d. Monter plusieurs étages par l'escalier	1	2	3
e. Monter un étage par l'escalier	1	2	3
f. Se pencher en avant, se mettre à genoux, s'accroupir	1	2	3
g. Marcher plus d'un km à pied	1	2	3
h. Marcher plusieurs centaines de mètres	1	2	3
i. Marcher une centaine de mètres	1	2	3
j. Prendre un bain, une douche ou s'habiller	1	2	3

10. Les questions qui suivent portent sur comment vous vous êtes senti(e) au cours de ces 4 dernières semaines. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée.
Au cours de ces 4 dernières semaines, y a-t-il eu des moments où :
(entourez la réponse de votre choix, une par ligne)

	En permanence	Très souvent	Souvent	Quelque fois	Rarement	Jamais
a. vous vous êtes senti(e) dynamique?	1	2	3	4	5	6
b. vous vous êtes senti(e) très nerveux(se)?	1	2	3	4	5	6
c. vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral?	1	2	3	4	5	6
d. vous vous êtes senti(e) calme et détendu(e)?	1	2	3	4	5	6
e. vous vous êtes senti(e) débordant(e) d'énergie?	1	2	3	4	5	6
f. vous vous êtes senti(e) triste et abattu(e)?	1	2	3	4	5	6
9. vous vous êtes senti(e) épuisé(e)?	1	2	3	4	5	6
h. vous vous êtes senti(e) heureux(se)?	1	2	3	4	5	6
i. vous vous êtes senti(e) fatigué(e)?	1	2	3	4	5	6

11. Indiquez pour chacune des phrases suivantes dans quelle mesure elles sont vraies ou fausses dans votre cas :
(entourez la réponse de votre choix , une par ligne)

	Totalement vrai	Plutôt vrai	Je ne sais pas	Plutôt fausse	Totalement fausse
a. Je tombe malade plus facilement que les autres	1	2	3	4	5
b. Je me porte aussi bien que n'importe qui	1	2	3	4	5
c. Je m'attends à ce que ma santé se dégrade	1	2	3	4	5
d. Je suis en excellent santé	1	2	3	4	5

Veuillez vérifier que vous avez bien fourni une réponse pour chacune des questions. Merci de votre collaboration.

18.12 APPENDIX 12 - EQ5D

EQ-5D

Health questionnaire
French version

Please indicate for each of the following topics, the statement that best describes your condition today, by checking the most appropriate box.

Mobility

I have no problem to get around on foot ☐
I have problems to get around on foot ☐
I have to stay in bed ☐

Autonomy

I have no problem taking care of me ☐
I have problems to wash or dress me alone ☐
I am unable to wash or dress me alone ☐

Day activities (eg work, study, housework, family or leisure activities)

I have no problem in carrying out routine activities ☐
I have problems in carrying out routine activities ☐
I am unable to perform routine activities ☐

Pain / discomfort

I have no pain or discomfort ☐
I have pain and / or moderate discomfort (s) ☐
I have pain and / or extreme discomfort (s) ☐

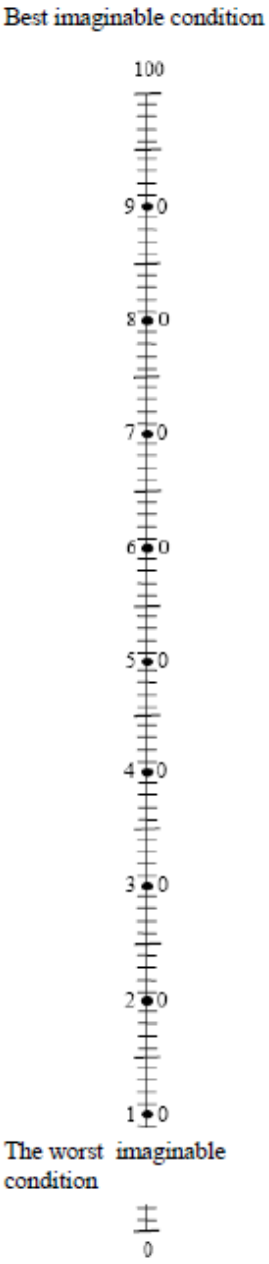
Anxiety depression

I am not anxious or depressed ☐
I am moderately anxious and / or depressed ☐
I am extremely anxious and / or depressed ☐

To help indicate how a particular state of health is good or bad, we have drawn a scale (like a thermometer) on which 100 is the best health you can imagine and 0 the worst health than you can imagine.

We would like you to indicate on this scale where you stand your health today. For this please draw a line from the box below to the point that, on the scale corresponds to your health today.

Your status Health Today



To the extent that all the answers are anonymous, it would be helpful to have some general information about each respondent to allow better interpretation of the answers. This is why we ask you to answer the following questions:

1. Have you had a serious illness? **Yes No** — TICK APPROPRIATE BOXES
   - Youself ☐ ☐
   - In your family ☐ ☐
   - Looking after others ☐ ☐

2. How old are you ? ☐ — TICK APPROPRIATE BOXES

3. Sexe : **Male Female** ☐ ☐

4. You smoke **Yes No** ☐ ☐ — TICK APPROPRIATE BOXES
   You stopped tosmoke ☐ ☐
   you never smoke ☐ ☐

5. Do you work or did you work **Yes No** ☐ ☐ — TICK APPROPRIATE BOXES
   In the sector of health or in social services ?
   If Yes, in what capacity?.....

6. Which of the following proposals, which one best describes your main activity? — TICK APPROPRIATE BOXES
   Employee or install to their account ☐
   Restated ☐
   Woman (man) at home ☐
   Student ☐
   Seeking employment ☐
   Other (please precised) ..... ☐
   .....

7. Do you continue your education beyond the compulsory school time? **Yes No** ☐ ☐ — TICK APPROPRIATE BOXES

8. Do you have a graduate graduate or qualification equivalent professional? **Yes No** ☐ ☐ — TICK APPROPRIATE BOXES

9. If you know the postcode of your location please enter here: ☐

EQ-5D

Questionnaire sur la santé Version Française

Veuillez indiquer, pour chacune des rubriques suivantes, l'affirmation qui décrit le mieux votre état de santé aujourd'hui, en cochant la case la plus appropriée.

Mobilité

Je n'ai aucun problème pour me déplacer à pied ☐

J'ai des problèmes pour me déplacer à pied ☐

Je suis obligé (e) de rester alité (e) ☐

Autonomie

Je n'ai aucun problème pour prendre soin de moi ☐

J'ai des problèmes pour me laver ou m'habiller tout (e) seul (e) ☐

Je suis incapable de me laver ou de m'habiller tout (e) seul (e) ☐

Activités courantes (exemples : travail, études, travaux domestiques, activités familiales ou loisirs)

Je n'ai aucun problème pour accomplir mes activités courantes ☐

J'ai des problèmes pour accomplir mes activités courantes ☐

Je suis incapable d'accomplir mes activités courantes ☐

Douleurs / gêne

Je n'ai ni douleur ni gêne ☐

J'ai des douleurs et/ou une gêne modérée (s) ☐

J'ai des douleurs et/ou une gêne extrême (s) ☐

Anxiété dépression

Je ne suis ni anxieux (se) ni déprimé (e) ☐

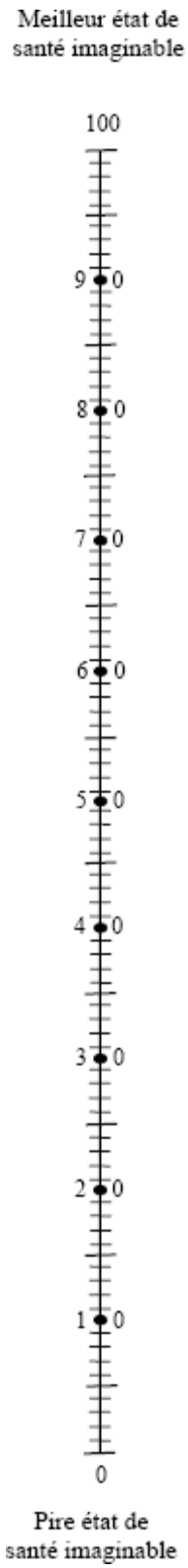
Je suis modérément anxieux (se) et / ou déprimé (e) ☐

Je suis extrêmement anxieux (se) et / ou déprimé (e) ☐

Pour vous aider à indiquer dans quelle mesure tel ou tel état de santé est bon ou mauvais, nous avons tracé une échelle graduée (comme celle d'un thermomètre) sur laquelle 100 correspond au meilleur état de santé que vous puissiez imaginer et 0 au pire état de santé que vous puissiez imaginer.

Nous aimerions que vous indiquiez sur cette échelle où vous situez votre état de santé aujourd'hui. Pour cela veuillez tracer une ligne allant de l'encadré ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de
santé aujourd'hui.

Votre état de Santé Aujourd'hui



Dans la mesure où toutes les réponses restent anonymes, il nous serait utile d'avoir quelques informations d'ordre général sur chaque personne interrogée afin de permettre une meilleure interprétation des réponses données. C'est pourquoi nous vous demandons de répondre aux questions suivantes :

1. Avez-vous vécu une grave maladie ? **Oui Non** — COCHEZ LES CASES APPROPRIEES
   - Vous-même ☐ ☐
   - Au sein de votre famille ☐ ☐
   - En soignant les autres ☐ ☐

2. Quel âge avez-vous ? ☐

3. Sexe : **Masculin Féminin** ☐ ☐ — COCHEZ LA CASE APPROPRIEE

4. Vous fumez **Oui** ☐
   Vous avez arrêté de fumer ☐
   Vous n'avez jamais fumé ☐ — COCHEZ LA CASE APPROPRIEE

5. Travaillez-vous ou avez-vous travaillé Dans le secteur de la santé ou dans des services sociaux ? **Oui Non** ☐ ☐ — COCHEZ LA CASE APPROPRIEE
   Si oui, à quel titre ?.....

6. Parmi les propositions suivantes, quelle est celle qui décrit le mieux votre activité principale ? — COCHEZ LA CASE APPROPRIEE
   Salarié(e) ou installé(e) à son compte ☐
   Retraité (e) ☐
   Femme (homme) au foyer ☐
   Etudiant (e) ☐
   En recherche d'emploi ☐
   Autre (veuillez préciser) ..... ☐
   .....

7. Avez-vous poursuivi vos études au-delà du temps de scolarité obligatoire ? **Oui Non** ☐ ☐ — COCHEZ LA CASE APPROPRIEE

8. Avez-vous un diplôme d'études supérieures ou une qualification professionnelle équivalente ? **Oui Non** ☐ ☐ — COCHEZ LA CASE APPROPRIEE

9. Si vous connaissez le code postal de votre lieu de résidence veuillez l'indiquez ici : ☐

18.13 APPENDIX 13 - ECOG

The index is usually used to describe the condition of the patient.

Grade	Description
0	Fully active - The patient can exercise his normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory up, can exercise an activity without significant physical constraints - light household activity, office, etc.
2	Ambulatory patient and able to take care of himself with personal care but unable to work or at home. Standing for more than 50% of the day.
3	Unable to make the minimum for personal care. Confined to bed or chair more than 50% of the day.
4	Completely disabled in his life, confined to bed or chair, requiring assistance for grooming and daily care.

18.14 APPENDIX 14 - TOXICITY ACCORDING TO CTCAE CRITERIA

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

18.15 APPENDIX 15 - TRANSPORT AND TRACEABILITY SHEET

Fiche de transport (UTC → Service de médecine interne)
Essai MSC-SLE – P150302J

FEUILLE DE TRANSPORT ET DE TRACABILITE

1. A compléter par l'Unité de Thérapie Cellulaire de l'AP-HP Saint Louis

EXPEDITION :

	DATE	HEURE
Départ :		

PATIENT RECEVEUR :
N° d'inclusion du patient : I__I__I__I - I__I__I__I__I - I__I - I__I Date de naissance : ___/____/_____

Type de Produit : Cellules stromales mésenchymateuses allogéniques issues de cordon ombilical

Produit allogénique issu du donneur :

Numéro de lot : _____

Volume : _____ Concentration : _____

EXPEDITEUR :	DESTINATAIRE :
Unité de Thérapie cellulaire, Hôpital Saint-Louis	*Service de médecine interne, UF04, hôpital Saint-Louis*

TRANSPORT:

Fiche de Transport : Conforme ☐ Non Conforme ☐	Personne Responsable	Signature

2. A compléter par l'Unité Clinique (service UF04 de Médecine Interne)

RECEPTION:

	DATE	HEURE	Personne Accusant Réception	Signature
Arrivée :				

Aspect du Produit Cellulaire :	Conforme ☐	Non Conforme ☐
Intégrité du système clos :	Conforme ☐	Non Conforme ☐
Etiquetage du produit :	Conforme ☐	Non Conforme ☐
Concordance des documents :	Conforme ☐	Non Conforme ☐
Transport a eu lieu entre 18-24°C :	Conforme ☐	Non Conforme ☐

Si non conforme, précisez :_____

INJECTION:

Date :

Numéro de lot : _____ **Contrôle ultime d'identité réalisé :** oui ☐ non ☐

	Heure Début	Heure Fin
Injection :		

Le temps total de l'injection est compris entre 30min et 1h : oui ☐ non ☐ Si non, précisez : _____

IDE Responsable du patient	Signature	Médecin Responsable du patient	Signature

OBSERVATIONS DANS LES 24 HEURES :

AUCUN incident à signaler : ☐ **Incident en cours d'injection :** ☐ **Incident RETARDE :** ☐

Hypotension/hypertension ☐ Frissons Hyperthermie ☐

Inflammation locale ☐ *Tachycardie/ bradycardie* ☐ Nausées/Vomissements ☐

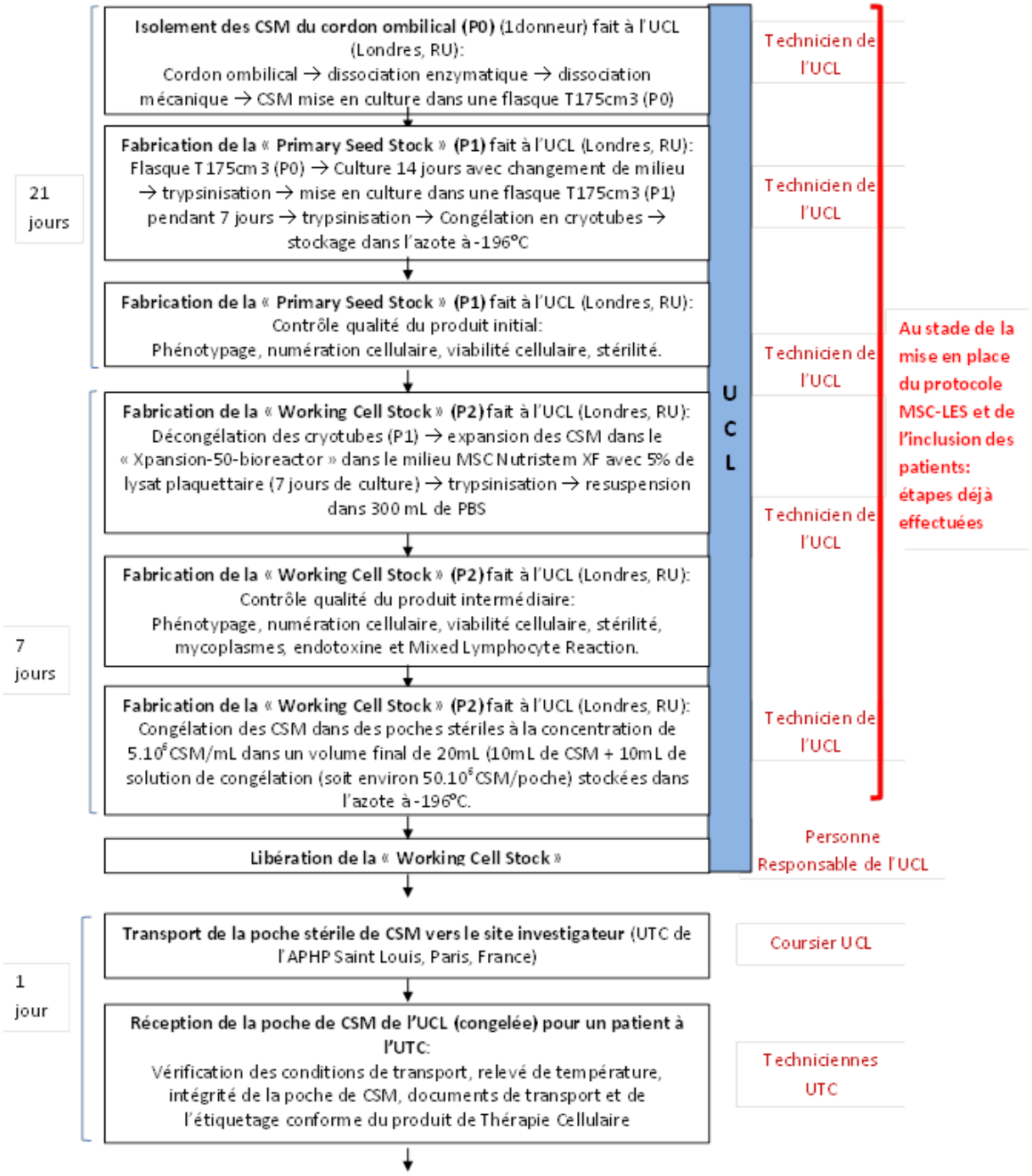
Autres symptômes : _____

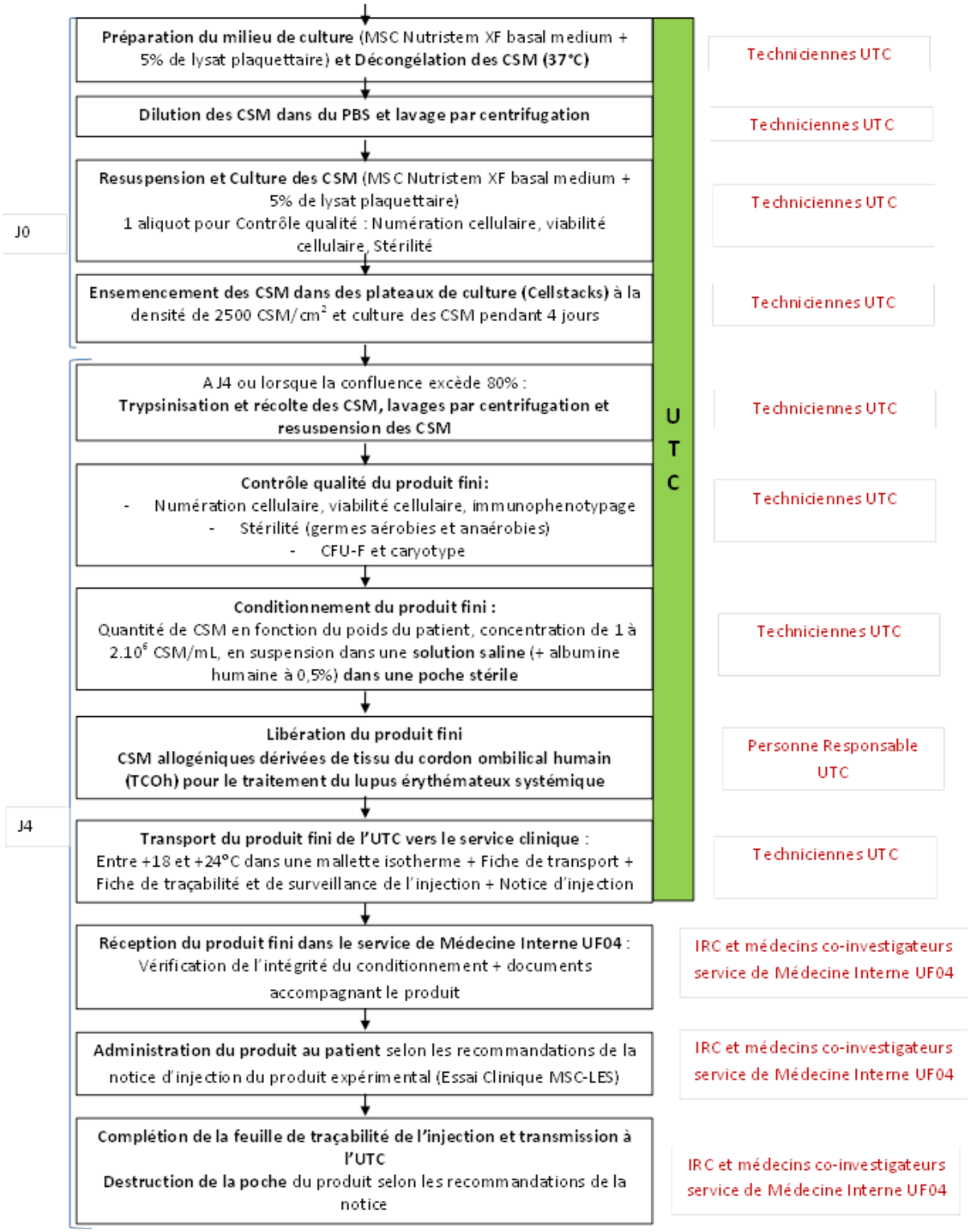
Feuille de transport et de traçabilité à faxer DANS LES 24 HEURES après injection à :

L'URC : fax 01 42 38 53 25

L'Unité de Thérapie Cellulaire : fax 01 42 49 47 55

18.16 APPENDIX 16 - CIRCUIT OF THE CELL THERAPY PRODUCT




Préparation du milieu de culture (MSC Nutristem XF basal medium + 5% de lysat plaquettaire) et Décongélation des CSM (37°C)
Techniciennes UTC
Dilution des CSM dans du PBS et lavage par centrifugation
Techniciennes UTC
Resuspension et Culture des CSM (MSC Nutristem XF basal medium + 5% de lysat plaquettaire)
1 aliquot pour Contrôle qualité : Numération cellulaire, viabilité cellulaire, Stérilité
J0
Techniciennes UTC
Ensemencement des CSM dans des plateaux de culture (Cellstacks) à la densité de 2500 CSM/cm² et culture des CSM pendant 4 jours
Techniciennes UTC
A J4 ou lorsque la confluence excède 80% :
Trypsinisation et récolte des CSM, lavages par centrifugation et resuspension des CSM
Techniciennes UTC
Contrôle qualité du produit fini:
- Numération cellulaire, viabilité cellulaire, immunophenotypage
- Stérilité (germes aérobies et anaérobies)
- CFU-F et caryotype
Techniciennes UTC
Conditionnement du produit fini :
Quantité de CSM en fonction du poids du patient, concentration de 1 à 2.10⁶ CSM/mL, en suspension dans une solution saline (+ albumine humaine à 0,5%) dans une poche stérile
Techniciennes UTC
Libération du produit fini
CSM allogéniques dérivées de tissu du cordon ombilical humain (TCOh) pour le traitement du lupus érythémateux systémique
Personne Responsable UTC
J4
Transport du produit fini de l'UTC vers le service clinique :
Entre +18 et +24°C dans une mallette isotherme + Fiche de transport + Fiche de traçabilité et de surveillance de l'injection + Notice d'injection
Techniciennes UTC
U T C
Réception du produit fini dans le service de Médecine Interne UF04 :
Vérification de l'intégrité du conditionnement + documents accompagnant le produit
IRC et médecins co-investigateurs service de Médecine Interne UF04
Administration du produit au patient selon les recommandations de la notice d'injection du produit expérimental (Essai Clinique MSC-LES)
IRC et médecins co-investigateurs service de Médecine Interne UF04
Complétion de la feuille de traçabilité de l'injection et transmission à l'UTC
Destruction de la poche du produit selon les recommandations de la notice
IRC et médecins co-investigateurs service de Médecine Interne UF04

18.17 APPENDIX 17 - WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

Appendix B: WHO toxicity parameters					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
GASTROINTESTINAL					
bilirubin	< 1,25 x N	1.26 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	> 10 x N
SGOT, SGPT	< 1,25 x N	1.26 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	> 10 x N
alkaline phosphatase	< 1,25 x N	1.26 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	> 10 x N
oral	no change	soreness, erythema	erythema, ulcers, can eat solids	ulcers, requires liquid diet only	alimentation not possible
nausea/vomiting	none	nausea	transient	vomiting requires therapy	intractable vomiting
diarrhea	none	transient < 2 days	tolerable but > 2 days	intolerable requiring therapy	hemorrhagic dehydration
constipation	none	mild	moderate	abdominal distention	distention and vomiting
RENAL					
urea	< 1,25 x N	1.26 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	> 10 x N
creatinine	< 1,25 x N	1.26 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	> 10 x N
proteinuria	none	1 + < 3 g/l	2 - 3 + 3 - 10 g/l	4 + > 10 g/l	nephrotic syndrome
hematuria	none	microscopic	gross	gross-clots	obstructive uropathy
CARDIAC					
arythmia	none	sinus tachyardia > 110 at rest	unifocal PVC atrial arrhythmia	multifocal PVC	ventricular tachycardia
function	none	asymptomatic but abnormal cardiac sign	transient symptomatic dysfunction, no therapy required	symptomatic dysfunction responsive to therapy	symptomatic dysfunction non-responsive to therapy
pericarditis	none	asymptomatic changes	symptomatic, no tap required	tamponade, tap required	tamponade, surgery required
NEUROTOXICITY					
consiousness	alert	transient lethargy	somnolence < 50 of waking hours	somnolence > 50 of waking hours	coma
peripheral	none	paresthesia and/or decreased tendon reflexes	severe paresthesia and/or mild weakness	intolerable paresthesia and/or marked motor loss	paralysis
PULMONARY	none	mild symptom	exertional dyspnea	dyspnea at rest	complete bed rest required
OTHERS					
fever	none	fever < 38 C	fever 38 - 40 C	fever > 40 C	fever with hypotension
headache	none	very mild	mild	moderate	severe
flu-like syndrome	none	very mild	mild	moderate	severe
flushing	none	very mild	mild	moderate	severe
vasculitis	none	restricted cutaneous	generalized cutaneous	hemorrhagic	systemic
allergic	no change	edema	bronchospasm	bronchospasm parenteral	anaphylaxis
cutaneous	no change	erythema	dry desquamation pruritus vesiculation	moist desquamation ulceration	exfoliative dermatitis, necrosis requiring surgical intervention
pain	none	mild	moderate	severe	intractable