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Phase II study of first line treatment of
Chronic Graft versus Host Disease with Arsenic Trioxide

GvHD-ATO Study
Protocol Number: GMED16-001

CLINICAL STUDY PROTOCOL

Development phase	II
Methodology	Prospective, national, multicenter, non-randomized study
Pathology	Chronic Graft versus Host Disease
Investigational product	Arsenic Trioxyde
Eudract N°	2016-002358-18
Version N°	7.0
Date	18th of December 2018
Sponsor	MEDSENIC 204, avenue de Colmar 67100 Strasbourg
Coordinator	Pr Mohamad MOHTY Service d'Hématologie Clinique Hôpital Saint Antoine AP-HP 75012 - Paris Cedex 12

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PARTICIPATION APPROVAL

I, Dr _____, investigator, confirm that I have read and understood the protocol .

I have fully discussed the objectives and procedures of the study with the sponsor representatives.

I will conduct the study in all respects in accordance with the study protocol and its amendments, and the ethical and regulatory principles.

Date: _____ Signature:

_____

SYNOPSIS

Sponsor :	MEDSENIC 204, avenue de Colmar F-67100 – Strasbourg
Title	Phase II study of first line treatment of Chronic Graft versus Host Disease with Arsenic Trioxide (GvHD-ATO Study)
Eudract Number	2016-002358-18
Coordinating investigator	Pr Mohamad MOHTY Centre Hospitalier Saint Antoine (AP-HP) Service d'Hématologie Clinique
Phase of development	Phase II
Objectives	*Main Objective* • To improve the response rate (complete and partial remission) at 6 months after diagnosis of chronic graft versus host disease (GvHD) and treatment with arsenic trioxide (ATO) in combination with prednisone with or without ciclosporine as a first line treatment *Secondary Objectives* • To evaluate failure-free survival (FFS), defined as death, recurrent or progressive malignancy, or initiation of a new systemic treatment for chronic GvHD • To decrease non-relapse mortality (NRM) of infectious and non-infectious origin • To improve overall survival (OS) and progression-free survival (PFS) • To spare patients from long-term use of corticosteroids (and their long-term side effects) • To improve quality of life self-reported by patient using the Lee Symptom Scale (LSS) and Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplantation subscale (FACT-BMT) • To evaluate tolerability and safety of ATO in combination with prednisone, with or without ciclosporine, in patients with chronic GvHD after allo-SCT
Study design	Prospective, national, multicenter, non-randomized

Number of patients planned	24 patients planned to be included in the study
Study centres	11 sites planned to participate to the study
Studied population	**Inclusion criteria** - Adult patients (≥18 years) who have received a first allogeneic stem cell transplantation for a hematological disease (any source of hematopoietic stem cells is authorized; any category of conditioning regimen prior to allo-SCT is authorized; any type of stem cell donors is authorized) - Confirmed diagnosis of a first episode of chronic GvHD requiring systemic immunosuppressive therapy (any prior GvHD prophylaxis previously used is accepted). Chronic GvHD diagnosis is defined according to the NIH Working Group Consensus. Chronic GvHD diagnosis will be based on the evaluation of the severity of the different clinical manifestations including: a/ Performance status evaluation b/ Cutaneous evaluation measured by the percentage of extension or the presence of sclerotic features. If relevant, confirmation with a biopsy should be performed whenever possible c/ Oral symptoms d/ Ocular symptoms e/ Gastro-intestinal symptoms f/ Evaluation of liver involvement (total bilirubin, transaminases and alkaline phosphatases) g/ Pulmonary function evaluation h/ Evaluation of the musculoskeletal manifestations, especially the amplitude of the relevant articulations i/ Genital tract symptoms - Signed informed consent - Absence of contra-indications to the use of ATO - Subjects affiliated with an appropriate social security system - Men must use a medically acceptable method of contraception throughout the treatment period and for at least 4 months and 10 days following the last treatment administration

Studied population	**Inclusion criteria *(con't)***
	- Women who are of childbearing potential must have a negative serum pregnancy test and agree to use a medically acceptable method of contraception throughout the study and for 3 months following the end of the study
	- Patient not participating or not having participated in a clinical study in the 30 days prior to his/her inclusion in the study
	
	Exclusion criteria
	- Patient developing acute GvHD (whether early or "late onset" form)
	- Patients developing overlap GvHD as defined by the 2015 NIH Working Group Consensus (presence of one or more acute GvHD manifestations in a patient with a diagnosis of chronic GvHD)
	- A "mild" form of chronic GvHD not requiring systemic immunosuppressive therapy
	- A "moderate" form of chronic GvHD limited to one organ site not requiring systemic immunosuppressive therapy
	- Patient receiving mycophenolate mofetil
	- Second allogeneic stem cell transplant
	- Severe cardiac diseases (congestive heart failure (NYHA class III), recent myocardial infarction (in the past 6 months before the inclusion), histories of unexplained syncope, …)
	- Significant arrhythmias, electrocardiogram (EKG) abnormalities:
	  - Congenital QT syndromes
	  - History or presence of significant ventricular or atrial tachyarrhythmia
	  - Clinically significant resting bradycardia (< 50 beats per minutes)
	  - QTc > 450 msec for men and > 470 msec for women on screening EKG (using the QTcF formula)
	  - Right bundle branch block plus left anterior hemiblock, bifascicular block
	- Central or peripheral neuropathy

	Exclusion criteria *(con't)* - Neutrophils < 0.5 × 109/L - Platelets < 50 × 109/L - Potassium ≤ 4 mEq/l* - Magnesium ≤ 1.8 mg/dl* - Calcium ≤ 2.15 mmol/l* - Hepatic impairment due to a suspected or proven liver damage, other than direct hepatic cGvHD involvement - PT < 50% - Renal impairment (creatinine ≥ 100 µmol/l) - Uncontrolled systemic infection which in the opinion of the investigator is associated with an increased risk of the patients' death within 1 month after the start of therapy - Severe neurological or psychiatric disorders - Denied informed consent - Pregnancy - Women breastfeeding at selection and throughout the treatment period * If abnormal at selection, to be corrected and re-validated following electrolytes infusion, before inclusion and each drug perfusion.

Investigational product	Arsenic trioxide 10 mg, concentrate for solution for infusion 1 mg/mL (aqueous sterile, clear, colorless). Arsenic trioxide is administrated either via the marketed product named TRISENOX® or the investigational medicinal product named ARSCIMED®. Patients under TRISENOX® treatment will not switch to ARSCIMED® treatment nor vice versa: - Patients already recruited and receiving TRISENOX® will continue receiving only TRISENOX® - All patients recruited after this amendment has been approved will receive ARSCIMED® only and not TRISENOX®. *Treatment scheme* As soon as the diagnosis of chronic GvHD requiring systemic immunosuppressive therapy is confirmed, patients will receive in addition to corticosteroids (prednisone) 1 mg/kg/day, with or without ciclosporine A, a daily infusion of ATO 0.15 mg/kg/day on days 1 to 5 (first week), 3 times per week during the second week (for example, days 8, 10 and 12), 2 times per week during the third week (for example, days 15 and 17) and one time during the fourth week (for example, day 24) (the latter four weeks represent one cycle). ATO should be administered within 10 days of starting prednisone at 1mg/kg/day for cGvHD treatment. Follow-up dates for response assessment and laboratory tests relate to the date of ATO infusion. Patients who are in partial response after the 1st cycle of ATO will be eligible to receive a second cycle of ATO infusions during 4 weeks (similar schedule to first cycle starting around day 60). In another word, a delay of 8 weeks to a maximum of 11 weeks (from the first infusion of ATO) will be observed between the two cycles of ATO therapy. Response definition is as follows: - Complete remission (CR) is defined as complete disappearance of any sign of chronic GvHD - Partial remission (PR) is defined as improvement of 1 or more point on a 4 to 7-point scale or an improvement of 2 or more points on a 10 to 12-points scale in at least 1 organ or site without progression in any other organ or site. For patients with Bronchiolitis Obliterans Syndrome (BOS), an absolute improvement in % FEV1 of 10% predicted or more (eg, 50% to 60%) is considered a PR as long as the initial % FEV1 is < 70%. Normalization (≥80%) is considered a CR. - Failure is defined as death, recurrent or progressive malignancy or the initiation of new systemic treatment for chronic GvHD. Increased dosing of existing treatment will not be considered as failure. Early failure is defined as failure within 2 weeks after the end of the first ATO cycle.

Investigational product *(con't)*	*Indications for secondary systemic treatment of chronic GvHD* Secondary systemic immunosuppressive treatment or other systemic treatment for control of chronic GvHD will be given at the discretion of the investigator in consultation with the GvHD team. In general, secondary systemic treatment is not indicated as long as there is continuing improvement in at least one manifestation of chronic GvHD and no progression of any other manifestations.
Study endpoints	*Primary endpoint* - Evaluation of response rate (complete and partial remission) of chronic GvHD at 6 months after diagnosis of chronic GvHD and treatment with arsenic trioxide (ATO) in combination with prednisone, with or without cyclosporine, as first line treatment *Secondary endpoints* - Percentage of patients with documented failure free survival (FFS), defined as death, recurrent or progressive malignancy, or the initiation of a new systemic treatment for chronic GvHD - Corticosteroids dosage and percentage of reduction in corticosteroids dosage at 6 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment - Cumulative incidence of transplant-related mortality (TRM) of infectious and non-infectious origin at 6 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment - OS and PFS at 6 and 12 months after diagnosis of chronic GvHD and treatment ATO as first line treatment - Descriptive analysis of quality of life parameters at inclusion, at 6 and 14 weeks, and at 6, 9 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment - Tolerability and safety of ATO in combination with prednisone, with or without cyclosporine, in patients with chronic GvHD after allo-SCT

Statistical methods	*Sample size calculation* Based on results from the literature, the hypothesis for the primary endpoint is an improvement in response rate (complete and partial remission) at 6 months after the diagnosis of chronic GvHD and start of corticosteroids, ATO, with or without cyclosporine, from 60% to 85%. Using a one step A Hern procedure (and anticipating a dropout rate around 10%), 24 (21+3) patients are needed (A'Hern RP, 2001). If the number of successful cases is 17 or more among the 21 patients, the hypothesis that the CR rate at 6 months is less than 60% is rejected with a target error rate of 0.05 (alpha probability). The beta probability in this case is 0.2. *Statistical analyses* Every patient included in the study and who has received at least one infusion of ATO will be taken into account at time of data analysis. A descriptive analysis will be conducted on the following parameters: - Patients and transplant characteristics - Primary and secondary endpoints Patients who do not receive any injection of ATO will not be analyzed and will be replaced to obtain 24 patients provided in the statistical analysis Qualitative data will be described in frequency and percentage and will be represented using histograms or diagrams of distribution. Quantitative data will be described using the calculations of average, standard deviation, median, and extreme values. The toxicities rate will be calculated and will be given with their 95% confidence intervals. The probabilities of survival will be estimated by the Kaplan-Meier method and by calculating the cumulative incidences for relapse/progression, and non-relapse mortality incidence.

Study Duration	The total duration of the study is expected to be 46 months (duration of recruitment: 34 months and study duration for a considered patient: 12 months).
Study Calendar	First patient first visit: September 2016 Last patient last visit: June 2020 Database lock: September 2020 Clinical study Report: November 2020

LIST OF ABBREVIATIONS

AAN	Antinuclear Antibody
AE	Adverse Event
Ag	Antigen
ALAT/SGPT	Alanine Amino-Transferase
Allo-SCT	Allogeneic Stem-Cell Transplantation
ANCA	Antineutrophil Cytoplasmic Antibody
ANSM	French National Health Authority
APC	Antigen Presenting Cells
APL	Acute Promyelocytic Leukemia
ASAT/SGOT	Aspartate Amino-Transferase
ASR	Annual Safety Report
ATC	Anatomic-Therapeutic-Chemical Classification
ATO	Arsenic Trioxide
ATRA	All-trans Retinoic Acid (tretinoin)
BAFF	B-cell Activation Factor
BCR	B-cell receptor
BOS	Bronchiolitis obliterans syndrome
BSA	Extent of Skin Involvement
CBC	Complete Blood Count
cGvHD	Chronic Graft Versus Host Disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CPP	Protection of Persons Committee
CR	Complete Remission
CsA	Cyclosporine A
CTC	Common Toxicity Criteria
DIBD	Development International Birth Date
DLI	Donor Lymphocytes Infusion
DNA	
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein Barr Virus
ECIL	European Conference on Infections in Leukemia
e-CRF	Electronic Case Report Form
EKG	Electrocardiogram
FACT-BMT	Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplantation subscale
FEV	Forced Expiratory Volume
FFS	Failure-free Survival
FORT	Free Oxygen Radicals Test
GCP	Good Clinical Practice
GGT	Gamma Glutamyl-Transferase

GHVD	Graft Versus Host Disease
GI	Gastro-intestinal
GMP	Good Manufacturing Practice
Hep	Hepatitis
HLA	Human Leucocyte Antigen
HR	Heart Rate
HY	Y-chromosome–encoded
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IL	Interleukine
IVIG	Intravenous Immunoglobulin
LSS	Lee Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
NRM	Non-relapse Mortality
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDC	Plasmacytoid Dendritic Cells
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free Survival
PFT	Pulmonary Function Tests
PML-RARa	Promyelocytic Leukemia-retinoic Acid Receptor-a
PR	Partial Remission
P-ROM	Photographic-range and Motion
PT	Prothrombin time
RIC	Reduced Intensity Conditioning
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAR	Serious Adverse Reactions
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TCR	T-cell receptor
TNBS	Trinitrobenzenesulfonic
Th	T-helper cell
TNF- α	Tumor Necrosis Factor
TRM	Transplant-related Mortality
WHO	World Health Organization

TABLE OF CONTENTS

1. Study rationale and background

Chronic Graft-versus-Host Disease (GvHD) is one of the most common and clinically significant complication affecting long-term survivors of allogeneic stem cell transplantation (allo-SCT). It is estimated that 30% to 70% of patients surviving more than 100 days will develop chronic GvHD (Lee and Flowers, 2008). Chronic GvHD is the cause of death in up to one third of all long-term survivors after transplantation for leukemia (Atkinson et al., 1990). Furthermore, chronic GvHD is consistently associated with decreased quality of life (Lee, 2005), impaired functional status, ongoing need for immunosuppressive medications and infectious complications. The chronic GvHD condition is clinically challenging and corticosteroids remain the only effective therapy.

1.1 Risk factors and treatment of chronic GvHD

Despite a global improvement in the outcome of patients undergoing allo-SCT, chronic GvHD continues to account for significant morbidity and mortality after allo-SCT. Although improvements have been made in the prevention of acute GvHD, these advances have not resulted in a concomitant decrease in the incidence of chronic GvHD (Lee*, et al* 2002). On the contrary, the CIBMTR recently reported an increase incidence of chronic GvHD in the recent years (Arai et al., 2015). Similarly, we have reported, in a single-center retrospective study, that the 5 years cumulative incidence of chronic GvHD has significantly increase between the 90' and the 2000s (Malard et al., 2014). This sustained incidence of chronic GvHD is likely related to changes in clinical allo-SCT practice (Malard et al., 2014). Allo-SCT is used in increasingly older patients, in whom the risk for chronic GvHD is greater. The use of unrelated donors and related but non HLA identical donors is expanding. Acute and chronic GvHD are larger problems, both in incidence and in severity, in recipients of alternative-donor allo-SCT.

The use of donor lymphocyte infusion (DLI) to treat relapsed disease or to achieve full donor chimerism after non-myeloablative transplantation has also resulted in the development of chronic GvHD in a substantial number of such patients. Patients receiving allogeneic peripheral blood stem cell transplants have a similar incidence of acute GvHD but a higher incidence of chronic GvHD than comparable patients receiving marrow grafts (Savani et al., 2016). Finally, used reduced intensity conditioning regimen, have been developed in order to reduce transplant-related toxicities, compared to classic myeloablative conditioning (Sengsayadeth et al., 2015). While, RIC regimens have succeeded to reduced non-relapse mortality, the incidence of chronic GvHD is not lower after RIC compared to myeloablative conditioning (Socie and Ritz, 2014). For these reasons, the number of patients with chronic GvHD continues to grow, and prevention or treatment of chronic GvHD must be considered one of the major obstacles still facing the field of blood and marrow transplantation.

Despite improvement in supportive care, most of chronic GvHD patients continue to have poor clinical function and altered quality of life. None of the present therapies for chronic GvHD (cGvHD) are successful in the majority of patients. Standard first line systemic treatment for cGvHD is orally administered corticosteroids (prednisolone 1 mg/Kg) and ciclosporine (Wolff et al., 2010). Over the past 10 years, alternative methods for the treatment of established chronic GvHD have been studied. Without treatment, less than 20% of patients with extensive chronic GvHD survive with Karnofsky performance scores >70%. On the other hand, long-term immunosuppressive treatment is generally required to control the disease (Lee and Flowers, 2008). Stewart et al. reported that the median duration of immunosuppressive treatment (corticosteroids + ciclosporine) was 23 months (Stewart et al., 2004). Interestingly, treatment was prolonged in patients who received peripheral blood stem cell transplant, in male patients with female donors and in those with HLA mismatched donors (Stewart et al., 2004).

Furthermore, in a randomized trial of immunosuppressive therapy for chronic GvHD, Koc et al. (Koc*, et al* 2002) reported the median duration of therapy with corticosteroids and ciclosporine was 1.6 years (range 0.3-8.2 years). The study further illustrated the difficulty in coming off all immunosuppression in chronic GvHD therapy. Despite dual immunosuppressive therapy, only 54% of patients were successfully weaned from immunosuppressive medications at 5 years and mortality directly attributable to chronic GvHD was 17% in the combination immunosuppressive arm. Finally, in this trial, addition of ciclosporine to corticosteroids was associated with a reduction in corticosteroid related morbidity, the incidence of avascular necrosis was 13% in the corticosteroids + ciclosporine arm compared to 22% in patients receiving corticosteroids alone (Koc*, et al* 2002).

Thus, treatment of this major complication remains a challenging issue that requires new and innovative approaches (Pavletic*, et al* 2006a). Attempts to identify novel agents or strategies to improve initial therapy for chronic GvHD have not improved on the combination of corticosteroids and a calcineurin inhibitor (Arora et al., 2001; Martin et al., 2009; Wolff et al., 2010). In addition, strategies to reduce the incidence of chronic GvHD have not reproducibly had beneficial effects. Failure to improve chronic GvHD prophylaxis and therapy can be partly attributed to an incomplete understanding of the pathophysiology of chronic GvHD.

Therefore, whether it is in the standard myeloablative allo-SCT setting or in the RIC allo-SCT setting, it is clear that advances in the therapy of chronic GvHD (a total of 1700 allo-transplants are performed every year in France with RIC allo-SCT representing >50% of all cases) are urgently required. Therapy with corticosteroids is often unrewarding and the toxicities from prolonged corticosteroid administration are great. With this steroid toxicity in mind, we believe that clinically meaningful endpoints for phase II testing of promising chronic GvHD drugs, may be whether their addition to high-dose corticosteroids would enable a higher response rate and successful corticosteroid taper.

1.2 Pathophysiology of chronic GvHD

Chronic GvHD emerges from alloreactive processes between donor-derived immune cells and host cell populations. While its pathophysiology is still poorly understood in contrast to that of acute GvHD, it is now evident that the clinical manifestations of cGvHD are the result of a highly complex immune pathology involving donor B cells and T cells as well as other cells.

Regarding B cells, it has been recognized since the early description of the disease that patients with cGvHD frequently have circulating antibodies that are reactive with recipient cells (Shimabukuro-Vornhagen et al., 2009). Two classes of recipient-reactive antibodies have been associated with cGvHD. The first class includes antibodies directed against antigens in the recipient that are not present in the donor. Antibodies directed against Y-chromosome–encoded (HY) proteins that develop in male patients who receive stem cell grafts from female donors exemplify this class of allo-antibodies. HY antibodies have been detected in more than 80% of patients with chronic GvHD but only in male recipients who had female donors (Miklos et al., 2005; Miklos et al., 2004; Zorn et al., 2004). HY antibodies very seldom develop in male recipients who have male donors. Anti-HY antibodies can be detected as soon as 3 months post-transplantation and seem to predict the subsequent development of chronic GvHD (Nakasone et al., 2015). Most studies of allo-antibodies have focused on HY antigens because male recipients who have female donors are relatively common compared with mismatches for autosomal epitopes. Nevertheless, antibodies specific for alloantigens derived from autosomal disparities have also been identified.

Antibodies directed against nonpolymorphic autoantigens represent a second class of antibodies frequently present in patients with chronic GvHD. For example, antibodies specific for platelet-derived growth factor receptor (PDGFR) have been described in patients with systemic sclerosis and chronic GvHD (Baroni et al., 2006; Svegliati et al., 2007).

These antibodies recognize native PDGFR, induce tyrosine phosphorylation and accumulation of reactive oxygen species (ROS), and stimulate type 1 collagen gene expression through the Ha-Ras-ERK1/2-ROS signaling pathway. The biologic activity of these autoantibodies thus suggests a role in the development of fibrosis. In addition to antibody production, accumulating evidence suggests that B cells contribute to the immune response by antibody-independent mechanisms such as antigen presentation, by production of cytokines and chemokines, and by acting as regulatory cells (Shimabukuro-Vornhagen et al., 2009). Low B-cell counts and increased risk of infections have long been recognized in patients with chronic GvHD. As in autoimmune diseases, distortion of normal B-cell homeostasis exists in chronic GvHD (Corre et al., 2010; Kuzmina et al., 2011; Sarantopoulos et al., 2007; Sarantopoulos et al., 2009). Patients with chronic GvHD have increased B-cell activation factor (BAFF)/B-cell ratios, delayed reconstitution of naive B cells, and increased numbers of pre-germinal center B cells. High levels of BAFF in the presence of low numbers of naive B cells have been proposed to foster the survival of activated alloreactive and autoreactive B cells, resulting in immune pathology (Sarantopoulos et al., 2007).

Donor T cells also clearly play an important role in the immune pathology of chronic GvHD. In humans, *in vivo* T-cell depletion is the only prophylactic measure that effectively decreases the incidence of cGvHD. Although early experimental studies have supported the paradigm of acute GvHD being a T-helper cell 1 (Th1) process and chronic GvHD being a T-helper cell 2 (Th2) process (Coghill et al., 2011), this old concept has been revisited, and recent data in humans suggest that Th1 (TC1)-Th17 responses are present in skin GvHD. The immune response occurring in chronic lichenoid GvHD showed a mixed Th1/Th17 signature with upregulated Th1/Th17 cytokine/chemokine transcripts and elevated numbers of interferon gamma– and interleukin 17 (IL-17) –producing $CD8^+$ T cells (Bruggen et al., 2014). Patients with active chronic GvHD also have a lower frequency of $CD4^+$ regulatory T cells (Tregs) when compared with patients without chronic GvHD (Bruggen et al., 2014; Matsuoka et al., 2010; Zorn et al., 2005).

The role of antigen presenting cells (APC) in chronic GvHD have also been recently emphasized by the observation that costimulation of donor T cells through CD80 or CD86 on either host or donor APC is necessary to induce chronic GvHD (Anderson et al., 2005). In particular, plasmacytoid dendritic cells (PDC) are involved in the pathophysiology of chronic GvHD, because the adoptive transfer of mature PDC exacerbate chronic GvHD, and they can stimulate donor T cells to trigger chronic GvHD in the absence of other APC (Koyama et al., 2009).

Thus, data in humans support a role of both T and B cells in a highly complex network leading to chronic GvHD. How these T- and B-cell networks interact has not been resolved.

1.3 Arsenic trioxide

Arsenic derivatives have been identified as compounds with therapeutic potential for over 2000 years in Greek and Chinese medicine. In the 1990s, researchers from China demonstrated complete clinical remissions in approximately 66% of patients with acute promyelocytic leukemia (APL) who received arsenic and a survival rate of 60% at 7 years (Zhang et al., 2000). At the same time, it was demonstrated that arsenic trioxide (As_2O_3 [ATO]) induced apoptosis in APL cells, interpreted as being through modulation of the promyelocytic leukemia-retinoic acid receptor-a (PML-RARa) fusion protein (Chen et al., 1996). The combination of ATO and oral all-trans retinoic acid (tretinoin [ATRA]) currently constitutes the standard of care for most patients with newly diagnosed and/or relapsed APL (de The et al., 1990). The use of ATO has also been explored in many other hematologic malignancies (Falchi et al., 2015) and in solid tumors (Subbarayan and Ardalan, 2014).

ATO has been initially investigated in 52 APL patients, previously treated with an anthracycline and a retinoid regimen, in two open-label, single-arm, non-comparative studies (Soignet et al., 2001; Soignet et al., 1998). One was a single investigator clinical study (n=12) and the other was a multicenter, 9-institution study (n=40). Patients in the first study received a median dose of 0.16 mg/kg/day of ATO (range 0.06 to 0.20 mg/kg/day) and patients in the multicenter study received a fixed dose of 0.15 mg/kg/day; ATO was administered intravenously over 1 to 2 hours until the bone marrow was free of leukaemic cells, up to a maximum of 60 days. Patients with complete remission received consolidation therapy with ATO for 25 additional doses over a 5 weeks period. Consolidation therapy began 6 weeks (range, 3-8) after induction in the single institution study and 4 weeks (range, 3-6) in the multicenter study. Complete remission rate were 92% and 85% in the single center and the multicenter study respectively. These results led to the approval of ATO for induction of remission and consolidation in adult patients with relapsed/refractory APL by the European Medicines Agency. ATO must be administered intravenously at a fixed dose of 0.15 mg/kg/day, given daily until the bone marrow remission is achieved (up to 50 days). Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. ATO is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks.

Arsenic Trioxide has been further evaluated for first line treatment of APL. A phase 3 multicenter trial compared ATRA + ATO (n=77), versus ATRA + chemotherapy (n=79) (Lo-Coco et al., 2013). ATO was administered intravenously at a fixed dose of 0.15 mg/kg/day, daily until complete remission (up to 60 days). Four courses of ATO consolidations were administered at 0.15 mg/kg/day, 5 days a week, 4 weeks on, 4 weeks off. Complete remission was achieved in all 77 patients in the ATRA–arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA–chemo- therapy group (95%) (P=0.12).

The ATRA + chemotherapy combination results in more frequent prolongation of cytopenias, mucositis, and infections, whereas the ATRA + ATO combination results in more frequent prolongation of the QTc interval and liver-function abnormalities.

As concerning its toxicity profile, ATO is usually well tolerated and its use is associated with a series of manageable adverse events including hyperleucocytosis, the APL differentiation syndrome, prolongation of the QT interval, peripheral neuropathy, mild myelosuppression, hyperglycemia and hypokalemia (Sanz et al., 2005). Of these, QT prolongation and, particularly, the so-called APL differentiation syndrome are the most serious ones as they can evolve into severe and potentially fatal ventricular arrhythmias (torsade de points) or respiratory failure, respectively. The APL differentiation syndrome is specific to APL as indicated by his name. Severe QT prolongation leading to fatal torsade de points has been reported in patients treated with locally formulated arsenic but never with arsenic trioxide used in clinical trials during post-marketing surveillance (Sanz et al., 2005; Unnikrishnan et al., 2001; Westervelt et al., 2001). However, stringent monitoring of serum electrolyte levels (K+ and Mg++) is recommended during therapy with ATO to minimize the risk of severe arrhythmias, particularly in patients receiving concomitant drugs that induce hypokalemia or hypomagnesemia.

1.4 Arsenic trioxide for chronic GvHD

The role of ATO has also been explored in murine models of autoimmune and autoinflammatory diseases. MRL/*lpr* mice develop a human lupus-like syndrome and, as in autoimmune lymphoproliferative syndrome, massive lymphoproliferation due to Fas-mediated apoptosis. In this model, mice developed cutaneous lesions, hypergammaglobulinemia and high levels of autoantibodies, including anti-DNA antibodies. Administration of ATO is able to achieve quasi-total regression of antibody- and cell-mediated manifestations in MRL/*lpr* mice (Bobe et al., 2006).

ATO eliminated, through activation of caspases, activated autoreactive T lymphocytes responsible for lymphoproliferation and skin, lung and kidney lesions, leading to significant prolonged survival rates. ATO also markedly reduced anti-DNA autoantibodies, rheumatoid factor, Interleukine IL-18, interferon gamma (IFN-γ), nitric oxide metabolite, Tumor necrosis factor alpha (TNF-α), Fas ligand, and IL-10 levels. Furthermore, ATO restored cellular reduced glutathione levels, thereby limiting the toxic effect of nitric oxide overproduced in MPR/*lpr* mice. Overall, ATO protected young mice from developing the syndrome and induced almost total disease disappearance in older affected mice.

Similarly, ATO has been evaluated in a TNBS-induced colitis model of inflammatory bowel disease (Singer et al., 2011). In this model, ATO used either in a preventive or curative mode markedly reduced the induced colitis, leading to prolonged mice survival. In addition, ATO was able to inhibit NF-κB expression and DNA-binding in colon extracts, leading to decreased cytokine gene expression (i.e. TNFα, IL-1β, IL-12, IL-17, IL-18 and IL-23). Furthermore, ATO reduced nitric oxide synthase and highly enhanced procaspase-3 and activated caspase-3, leading to neutrophil elimination.

ATO has also proven to be effective in a murine model of systemic sclerosis, another autoimmune disease (Kavian et al., 2012b). In this model, ATO inhibited the production of autoantibodies and was associated with a clinical benefit, as shown by the reduced skin and lung fibrosis. These beneficial effects were mediated through reactive oxygen species (ROS) generation that selectively killed activated pathogenic fibroblast containing low levels of glutathione.

Chronic GvHD presents clinical features that mimic autoimmune diseases such as systemic sclerosis, lupus erythematosus or Sjögren syndrome, and autoimmune-like manifestations are a defining characteristic of cGvHD. The effectiveness of ATO in murine models of autoimmune disease has prompted evaluation of ATO in murine model of chronic GvHD (Kavian et al., 2012a).

Sclerodermatous chronic GvHD was induced in BALB/c mice by body irradiation, followed by B10.D2 bone marrow and spleen cell transplantation. Mice were simultaneously treated with daily intra-peritoneal injections of ATO. While transplanted mice displayed severe clinical symptoms (diarrhea, alopecia, vasculitis, and fibrosis of the skin and visceral organs), the symptoms were dramatically abrogated in mice treated with ATO. Treatment with ATO was associated with a decrease percentage of CD4+ T cells and PDC. Furthermore, IL-4, a Th2 related cytokine and IL-17, a Th17 related cytokine and autoantibodies were significantly reduced in mice treated with ATO. These beneficial effects were mediated through the depletion of glutathione and the overproduction of H_2O_2 that killed activated $CD4^+$ T cells and PDC.

From the above studies, it appears that ATO is administered routinely and safely to patients with hematologic malignancies. The effectiveness of ATO in human APL patients and in the mice models of autoimmune diseases have in common targeting of the cells involved in these different diseases by inducing their apoptosis. In a murine model of chronic GvHD, ATO effect was mediated through the depletion of glutathione and the overproduction of H_2O_2 that killed activated $CD4^+$ T cells, in particular Th17 cells, and PDC, two key cells in chronic GvHD pathophysiology initiation. Furthermore, autoantibody production was also inhibited by ATO in this model, suggesting that ATO also trigger B cells mediated chronic GvHD.

This leads to the hypothesis that ATO delivered early at diagnosis of chronic GvHD will be an effective treatment. To test this hypothesis, we propose this study of ATO in combination with ciclosporine-A and corticosteroids as first line therapy for newly diagnosed chronic GvHD after allo-SCT. We hypothesize the addition of ATO to prednisone and ciclosporine-A for the initial treatment of chronic GvHD will increase the overall response rate, and enable a more rapid and effective corticosteroids taper.

2. Study Objectives

2.1 Primary Objective

The primary objective is to improve the response rate (complete and partial remission) at 6 months after diagnosis of chronic GvHD and treatment with arsenic trioxide (ATO) in combination with prednisone with or without ciclosporine as first line treatment.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate failure-free survival (FFS), defined as death, recurrent or progressive malignancy, or initiation of a new systemic treatment for chronic GvHD
- To decrease non-relapse mortality (NRM) of infectious and non-infectious origin
- To improve overall survival (OS) and progression-free survival (PFS)
- To spare patients from long-term use of corticosteroids (and their long-term side effects)
- To improve quality of life self-reported by patient using the Lee Symptom Scale (LSS) and Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplantation subscale (FACT-BMT)
- To evaluate tolerability and safety of ATO in combination with prednisone, with or without ciclosporine, in patients with chronic GvHD after allo-SCT

3. Study design

This is a prospective, national, multicenter, non-randomized Phase II study that will include a total number of 24 patients.

The duration of participation planned is as follows:

- Duration of recruitment: 34 months
- Study duration for a considered patient: 12 months
- Total duration of the study: 46 months

Several visits are scheduled in the study as follows:

- At the time of diagnosis for the screening visit
- Follow-up visits to be performed every week during ATO treatment
- Follow-up visits to be performed every 2 weeks from second to third month of ATO treatment
- Follow-up visits to be performed every month from the fourth to sixth month of ATO treatment
- Follow-up visits to be performed every 3 months: at 9 months and 12 months (final visit)

Arsenic trioxide is administrated either via the marketed product named TRISENOX® or the investigational medicinal product named ARSCIMED® (Cf. section 5 for more detail).

4. Patients selection

4.1 Inclusion criteria

Patient will be eligible for inclusion in this study if the patient met all the following criteria:

- Adult patients (≥18 years) who have received a first allogeneic stem cell transplantation for a hematological disease (any source of hematopoietic stem cells is authorized; any category of conditioning regimen prior to allo-SCT is authorized; any type of stem cell donors is authorized)
- Confirmed diagnosis of first episode of chronic GvHD requiring systemic immunosuppressive therapy (any prior GvHD prophylaxis previously used is accepted). Chronic GvHD diagnosis is defined according to the National Institutes of Health (NIH) Working Group Consensus. Chronic GvHD diagnosis will be based on the evaluation of the severity of the different clinical manifestations including:

  a/ Performance status evaluation

  b/ Cutaneous evaluation measured by the percentage of extension or the presence of sclerotic features. If relevant, confirmation with a biopsy should be performed whenever possible

  c/ Oral symptoms

  d/ Ocular symptoms

  e/ Gastro-intestinal symptoms

  f/ Evaluation of liver involvement (total bilirubin, transaminases and alkaline phosphatases)

  g/ Pulmonary function evaluation

  h/ Evaluation of the musculoskeletal manifestations, especially the amplitude of the relevant articulations

  i/ Genital tract symptoms
- Signed informed consent (see Appendix 14)
- Absence of contra-indications to the use of ATO

- Subjects affiliated with an appropriate social security system
- Men must use a medically acceptable method of contraception throughout the treatment period and for at least 4 months and 10 days following the last treatment administration
- Women who are of childbearing potential must have a negative serum pregnancy test and agree to use a medically acceptable method of contraception throughout the study and for 3 months following the end of the study
- Patient not participating or not having participated in a clinical study in the 30 days prior to his/her inclusion in the study

4.2 Exclusion criteria

Patients fulfilling ONE or MORE of the following criteria will not be included in the study:

- Patient developing acute GvHD (whether early or "late onset" form)
- Patients developing overlap GvHD as defined by the 2015 NIH Working Group Consensus (presence of one or more acute GvHD manifestation in a patient with a diagnosis of chronic GvHD)
- A "mild" form of chronic GvHD not requiring systemic immunosuppressive therapy
- A "moderate" form of chronic GvHD limited to one organ site not requiring systemic immunosuppressive therapy
- Patient receiving mycophenolate mofetil
- Second allogeneic stem cell transplant
- Severe cardiac diseases (congestive heart failure (NYHA class III), recent myocardial infarction (in the past 6 months before the inclusion), histories of unexplained syncope, …)

- Significant arrhythmias, EKG abnormalities:
  - Congenital QT syndromes
  - History or presence of significant ventricular or atrial tachyarrhythmia
  - Clinically significant resting bradycardia (<50 beats per minutes)
  - QTc > 450 msec for men and > 470 msec for women on screening EKG (using the QTcF formula, in Section 11.8)
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
- Central or peripheral neuropathy
- Neutrophils $< 0.5 \times 10^9$/L
- Platelets $< 50 \times 10^9$/L
- Potassium ≤ 4 mEq/l*
- Magnesium ≤ 1.8 mg/dl*
- Calcium ≤ 2.15 mmol/l*
- Hepatic impairment due to a suspected or proven liver damage, other than direct hepatic cGvHD involvement
- PT < 50%
- Renal impairment (creatinine ≥ 100 µmol/l)
- Uncontrolled systemic infection which in the opinion of the investigator is associated with an increased risk of the patients death within 1 month after the start of therapy
- Severe neurological or psychiatric disorders
- Denied informed consent
- Pregnancy
- Women breastfeeding at selection and throughout the treatment period

* If abnormal at selection, to be corrected and re-validated following electrolytes infusion, before inclusion and each drug perfusion.

4.3 Withdrawal/premature discontinuation criteria

A premature discontinuation is defined when a patient selected in a study ceases his/her participation before the end of study.

The criteria for premature discontinuation of the study are:

- Withdrawal of informed consent
- Lost to follow-up
- Occurrence of AE/SAE
- Inclusion criteria not met requiring premature discontinuation
- Protocol deviation
- Other reason

Patients who do not receive any injection of ATO will not be analyzed and will be replaced to obtain the total 24 patients required in the statistical analysis.

5. Study treatment

5.1. Description of study treatment

Arsenic trioxide (ATO) is administrated either *via* a marketed product, i.e. TRISENOX®, or an Investigational Medicinal Product, i.e. ARSCIMED®.

TRISENOX® was administered to patients from the start of the clinical trial. ARSCIMED® will be administered to patients included in the clinical trial after approval from the ANSM for its use in this clinical trial. Patients under TRISENOX® treatment will not switch to ARSCIMED® treatment nor vice versa.

- All patients already included in the trial and who received TRISENOX® will continue with TRISENOX® until completion of their participation in the clinical trial.
- All patients recruited after this amendment has been approved will receive ARSCIMED® only and not TRISENOX®.

TRISENOX® and ARSCIMED® have the same active substance, excipients, dosage form and route of administration (Summary of Product Characteristics (Trisenox)) and Investigator brochure (ARSCIMED®) for details) and are considered equivalent. The decision in switching to ARSCIMED® during the clinical trial is based on the fact that the availability of ARSCIMED®, treatment being developed by MEDSENIC in the population included in this trial, will avoid repeated and further impact on recruitment in the study related to any further supply disruptions of TRISENOX®, as it occurred in 2014 and again in 2017.

Both formulations (TRISENOX® and ARSCIMED®) are adjusted to pH 8 with dilute hydrochloric acid. Whereas TRISENOX® is manufactured by TEVA and supplied as a glass ampoule; ARSCIMED® is manufactured by IRPF[1]-Toulouse and supplied as a glass vial. Further information on ARSCIMED® is available in the Investigational Medical Product Dossier of this product.

[1] Institut de Recherche Pierre Fabre

The investigational medication has the following characteristics:

- ATC code: L01XX27
- Pharmacotherapeutic group: other antineoplastic agents
- Form/Presentation: concentrate for solution for intravenous infusion / 1 mg/1 mL / 10 mL
- Excipients: sodium hydroxide, hydrochloric acid as pH adjuster and water for injections
- Administration:

  - 0,15 mg/kg/infusion on days 1 to 5 (first week), 3 times per week during the second week (for example, days 8, 10 and 12), 2 times per week during the third week (for example, days 15 and 17) and one time during the fourth week (for example, day 24), in addition to ciclosporine A (if relevant) and corticosteroids. The latter four weeks represent one cycle of 11 administrations.

  - Must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalized at the beginning of treatment due to ensure adequate monitoring.

  - Aseptic technique must be strictly observed throughout handling of ATO since no preservative is present.

- Must be diluted with 100 to 250 mL of glucose 50 mg/mL (5%) solution for injection or sodium chloride 9 mg/mL (0.9%) solution for injection immediately after withdrawal from the ampoule for single use only. Unused portions of each ampoule must be discarded properly. Unused portions for later administration must not be saved.
- Must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.
- The diluted solution must be clear and colorless. All parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration. The preparation must not be used if foreign particulate matter is present.
- Should be administered within 10 days of starting prednisone at 1mg/kg/day for cGvHD treatment. Treatment with persistent prednisone (or equivalent) at doses lower than 1 mg/kg/day at the time of enrollment is allowed (i.e patient was treated for acute GvHD with prednisone and developed evolving chronic GvHD).
- A delay of 8 weeks to a maximum of 11 weeks (from the first infusion of ATO) will be observed between the two cycles of ATO therapy.

5.2.Labelling and packaging of study treatment

Packaging and labeling will be in accordance with Good Manufacturing Practice (GMP) for clinical trials.

- ATO (TRISENOX®) is a commercial product with a marketing authorization for a type of acute myeloid leukaemia called acute promyelocytic leukaemia (APL). At each inclusion of a patient in the study, ATO (TRISENOX®) will be bought by the central pharmacy of the hospital. One box contains 10 ampoules containing 10 mL of a sterile, clear, colorless solution (1 mg arsenic trioxide/1 mL). At reception of product by the central pharmacy of the hospital, the boxes will be identified by labels which will include the information required in the Annex 13 of the Volume 4 of "The rules governing medicinal products in the European Union" (current EU GMP practices).

- ATO (ARSCIMED®) will be sent by the manufacturer on behalf of the Sponsor to the central pharmacy of the hospital at each inclusion of a patient in the study. One box contains 11 vials containing 10 mL of a sterile, clear, colorless solution (1 mg arsenic trioxide/1 mL). No identification of boxes by labels is performed at reception of the product because labeling is already ensured by the manufacturer in accordance with the Annex 13 of the Volume 4 of "The rules governing medicinal products in the European Union" (current EU GMP practices).
- The traceability of the therapeutic units will be ensured by the standard procedures of the pharmacy and the management of product will be monitored regularly.
- Depending on the patient weight and the number of cycles, the number of vials required will be 11, 22 or 44.
- TRISENOX® and ARSCIMED® must not be used beyond expiration date printed on the label.

5.3.Handling and accountability of study treatment

At each inclusion of a patient in the study, ATO (TRISENOX®) will be bought by the central pharmacy of the hospital concerned with a medical prescription written by the principal investigator. Once introduced in the study and at each inclusion of a patient in the study, ATO (ARSCIMED®) will be provided to the central pharmacy of the hospital by the IRPF (Institut de Recherche Pierre Fabre, manufacturer mandated by the sponsor).

The investigator and the study site are responsible for investigational product accountability. To this end, it is assumed that all clinical study supplies will be delivered to and by the responsibility of a suitably qualified and authorized person such as a hospital pharmacist, who will document drug disposition and accountability for the duration of the study.

Investigators and pharmacists should note that the clinical study supplies may only be used for the clinical study for which they are indicated. They must not be employed for any other study or for any other clinical use.
Except for ATO, the investigational drug, all other drugs used in this study will be taken from the normal stocks of each participating centre.
Inventory records must be readily available and must include at least the following information: quantities, dates, batch number, expiration date, study code number, and patient identification numbers.
In the context of this study, the preparation of ATO, the packaging, the labelling and batch release will be undertaken by the pharmacy of each participating centre.

ATO (ARSCIMED®) will be provided to the clinical site as already packaged, labeled and released.

All unused and/or partially used study drugs will be kept by the central pharmacy of the hospital concerned upon completion or termination of the study at the latest. At the study end, the unused vials will be collected by a provider designated by the Sponsor.

5.4.Conditions for storage of study treatment

TRISENOX® and ARSCIMED® will be stored in a secure location at 25°C (77°F); excursions will be permitted to 15-30°C (59-86°F), but TRISENOX® must not be frozen and ARSCIMED® must not be refrigerated or frozen.

After dilution of TRISENOX® in intravenous solutions, ATO is chemically and physically stable for 24 hours at 15-30°C and 48 hours at refrigerated (2-8°C) temperatures. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

After dilution of ARSCIMED® in intravenous solutions, ATO is chemically and physically stable for 4 hours at 15-25°C. The product must not be stored at refrigerated (2-8°C) temperatures after dilution since its stability under these conditions has not been studied yet. From a microbiological point of view, the product must be used

immediately.

6. Concomitant treatments

6.1. Ciclosporine A

- Ciclosporine A will be delivered using local standard criteria, (if relevant). However:

- Ciclosporine level should lie within the therapeutic range (i.e. 200-400 ng/mL): to harmonize CsA target levels
- Ciclosporine-induced renal insufficiency should lead to dose adjustment and even temporary withdrawal of the drug

- Suggested guidelines for initial dose of Ciclosporine A:

Oral administration of ciclosporine should continue for patients who are being treated with ciclosporine at the time of enrolment, or if it is relevant, the administration should commence initially at 6mg/kg daily.

- Monitoring of ciclosporine level:

- Concentrations of ciclosporine in the plasma may be monitored at the discretion of the investigator. Dose adjustments may be made to maintain ciclosporine concentrations at 200-400 ng/ml. Monitoring may be especially helpful in patients with renal impairment and in patients being treated with medications that may affect the concentration of ciclosporine.
- Medications that could increase the concentration of ciclosporine include diltiazem, nicardipine, verapamil, metoclopramide, ketoconazole, fluconazole, itraconazole, erythromycin and methylprednisolone.
- Medications that could decrease the concentration of ciclosporine include rifampycin, phenytoin, phenobarbital and carbamazepine.

- Deviations from guidelines for administration of ciclosporine

  Deviations from the above guidelines may be made at the discretion of the investigator in consultation with the transplant centre. Toxicity associated with the administration of ciclosporine may require dose adjustments, which should be managed according to individual transplant centre practice.

6.2.Prednisone

- The initial dose of prednisone is 1.0 mg/kg/day, this dose should be maintained for 2 weeks, after which a tapering schedule should commence up until response assessment at 6 weeks, after which treatment is as follows:

- CR: continue tapering of Prednisone dose (see Table below)
- No CR: maintain Prednisone dose at 1 mg/kg/day on alternate days or 0.5 mg/kg/day every day

  Usual prevention of steroid-induced gastro-intestinal (GI) side effect should be given (omeprazole or other drugs, according to local practice).

- The investigator will determine the regimen for administration of prednisone after enrolment in the study. The following taper schedule is given as a general guideline:

Table 1 : <u>Prednisone Taper Schedule</u>

Week	Dose (mg/kg actual body weight/day)
0	1.0 qod
2	0.75 qod
4	0.65 qod
6	0.50 qod (if CR, continued tapering of corticosteroids dose) 0.50 qod (if No CR, maintain this dose until resolution of all reversible clinical manifestations or adjust the required dose)
8	0.40 qod
10	0.30 qod
12	0.20 qod
14	0.15 qod
20	0.0

- The investigator should examine the patient before each reduction in the dose of prednisone. If there is exacerbation or recurrence of chronic GvHD at any step of the taper, the dose of prednisone should be increased by 2 levels with daily administration for 2-4 weeks, followed by resumption of alternate day administration. Prednisone may be discontinued after 2 weeks of treatment at a dose of 0.15 mg/kg every other day. Qod prednisone dosing is not required, and the use of qod dosing is at the discretion of the investigator. It is suggested, but not required, that patients taper off steroids before tapering of other immunosuppressive medications.
- Toxicity associated with the administration of prednisone should be managed according to individual transplant center practice.

6.3.Preventive treatments for infections

- Antibiotic prophylaxis for prevention of Pneumocystis pneumonia and infections with encapsulated organisms must be given to all patients until 6 months after discontinuation of all systemic immunosuppressive treatment. Suggested antibiotic regimens are: Trimethoprim/Sulfamethoxazole DS 1 tab PO qMWF, or if sulfa allergic, Atovaquone 1500 mg PO qMWF or Pentamidine 300 mg inhaled q4 weeks. Additional prophylactic antibiotics are at the discretion of the physician.
- Prophylactic antiviral and antifungal medications must also be given until the steroid dose is stable < 0.15 mg/kg/day. All patients who are at risk of CMV infection should be monitored for occult CMV infection, and appropriate treatment should be instituted per institutional practice. Populations at risk of CMV infection include all CMV-seropositive patients, all CMV-seronegative patients with CMV-seropositive donors, and all patients receiving blood product transfusions from CMV-seropositive donors.
- Antifungal prophylaxis: No specific antifungal prophylaxis is recommended. In case it is the routine policy of a centre to give an antifungal prophylaxis in patients with chronic GvHD (i.e., fluconazole, oral amphotericin B, itraconazole, posaconazole or other drugs for which there are published data of controlled trials showing the antifungal prophylaxis of this drug in allo-SCT patients), it is required that this policy is being documented in the CRF and the same policy be applied to all the patients included in the centre.
- In all cases, physicians can refer to the recommendations made by the European Conference on Infections in Leukemia (ECIL). The full version is available on the website of the EBMT:
https://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx
- All treatments given for prevention of infectious complications must be reported in the electronic CRF of the study.

6.4.Prohibited concomitant treatments

- Patient receiving mycophenolate mofetil
- Any other investigational study drugs than ATO

7. Study procedures: inclusion procedure, treatment schema and calendar of evaluations

Patients will undergo the procedures and examinations which must be performed as shown in the following flow chart:

Table 2. Study Summary

	Selection (V1) (10 days before ATO treatment)	During ATO treatment (1st and 2nd cycles)	Every 2 weeks (from M2 to M3) +/- 5 days	Every month (M4, M5, M6) +/- 5 days	At 6 and 14 weeks and every 3 months (M6, M9, M12) +/- 5 days	Study drop-out +/- 5 days
Information and patient consent	*					
Inclusion/exclusion criteria check	*					
Socio-demographics	*					
Concomitant diseases	*					
Recipient, Donor and Transplant characteristics[10]	*					
Diagnosis & Scoring of chronic GvHD	*					
Chronic GvHD activity assessment form A	*				*	*
Chronic GvHD activity assessment form B	*				*	*
Lee Symptom scale	*				*	*
FACT-BMT	*				*	*
Physical examination	*	*[1]	*	*	*	*
EKG – QTc[1] measurement	*	*[1]	*			
Hematology[3]	*	*[9]	*	*	*	*
Biochemistry[4]	*	*[2/9]	*	*	*	*
Coagulation test[5]	*	*[9]	*	*	*	*
Infectious disease surveillance	*	*[2]		*	*	*
Serum immunoglobulin level	*			*	*	*

Table 2. Study Summary *(continued)*

	Selection (V1) (10 days before ATO treatment)	During ATO treatment (1st and 2nd cycles)	Every 2 weeks (from M2 to M3) +/- 5 days	Every month (M4, M5, M6) +/- 5 days	At 6 and 14 weeks and every 3 months (M6, M9, M12) +/- 5 days	Study drop-out +/- 5 days
Autoantibodies (AAN, ANCA)	*	*[2]		*	*	*
Serum pregnancy test	*					
Immunological evaluation (Saint Antoine)	*	*			*	*
Pharmacokinetic evaluation		*[6]				
Pulmonary function test (FEV1)	*				*	*
Chest x-ray	*					
Cutaneous biopsy *(if relevant)*	*					
ATO treatment (*date, dose, reason of change*)		*				
Response to treatment					*	
Associated treatment(s)[8]	*[7]	*	*	*	*	*
Adverse event(s)		*	*	*	*	*

[1] During ATO treatment, must be performed daily before each ATO administration.
[2] Must be performed weekly.
[3] CBC included leucocytes, neutrophils, lymphocytes, monocytes, and eosinophils counts, hemoglobin and platelets.
[4] Biochemistry included measurement of glycaemia[9], creatinine[1], uric acid, calcium[1], potassium[1], magnesium[1], total protein, albumin, total bilirubin, alkaline phosphatases, SGOT[9], SGPT[9], and LDH.
[5] Prothrombin time [PT], activated partial thromboplastin time [APTT].
[6] Pharmacokinetic evaluation: the samples must be performed before each administration at D2, D3, D4, D5, D8, D12, D17 and D24 of cycle 1 and cycle 2 (if applicable).
[7] History of GvHD prophylaxis : documentation of any associated treatments and topical therapy since graft for acute GvHD or progressive form of cGvHD treated by corticotherapy < 1 mg/kg/day, whenever possible given collected clinical history
[8] Documentation of any associated treatments and topical therapy for chronic GvHD (including glucocorticoid creams, topical tacrolimus, oral beclomethasone or budesonide, topical azathioprine and ophthalmic glucocorticoids…)
[9] Must be performed twice a week.
[10] Documentation on the diagnosis of hemopathy requiring transplant and DLI modality.

7.1 Patients selection

Only patients meeting the National Institutes of Health (NIH) criteria for chronic GvHD requiring systemic therapy are eligible for inclusion in this study (Jagasia et al., 2015) (see Appendix 1 for full details).

Allogeneic stem cell recipients who develop a first episode of chronic GvHD will be screened for eligibility. If they fulfill inclusion and exclusion criteria and give their informed consent (see Appendix 14), they will be included in the study.

7.1.1 Diagnosis of chronic GvHD

Minimum one diagnostic manifestation of chronic GvHD OR presence of at least 1 distinctive manifestation plus a pertinent biopsy, laboratory, or other tests (eg, pulmonary function tests [PFT], Schirmer's test), evaluation by a specialist (ophthalmologist, gynecologist), or radiographic imaging showing chronic GvHD in the same or another organ, unless stated otherwise (see Appendix 1 and Appendix 2).

Differential diagnosis of chronic GvHD must be excluded e.g. toxicity, infection.

Diagnostic and distinctive manifestations of chronic GvHD can be found in the skin and appendages, mouth, eyes, genitalia, esophagus, lungs, and connective tissues. Biopsy or other testing is often valuable to confirm the presence of chronic GvHD, but is not always feasible and is not mandatory if the patient has at least one of the diagnostic findings of chronic GvHD. Thus, organ biopsies are per physician discretion.

7.1.2 Definition of mild, moderate and severe chronic GvHD

Eight organs or sites (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joint and fascia, and genital tract) are considered for calculating global score. Elements included in the proposed global scoring include both the number of organs or sites involved and the severity score within each affected organ. Performance status scoring is not incorporated into the global scoring system. Organ scoring is performed according to the NIH Working Group consensus (Jagasia et al., 2015) (see Appendix 2).

For skin, the composite score is split into 2 scores to document the extent of skin involvement (BSA) and the specific skin features, separately (see Appendix **6**).The higher of the 2 scores is to be used for computation of global severity.

Eyes, are better assessed by a specialist, however, it is not mandatory.

For lung, pulmonary function tests to assess the first forced expiratory volume (FEV1) are mandatory in this protocol. The composite score is split in 2 score, a symptom score and a FEV1 score based. In case of discrepancy between both score, the FEV1 score is used for the final lung scoring.

For genital tract, scoring is based on severity of the signs instead of symptoms, both in man and woman, according to the figure provided in Appendix 3. Genital tract scoring must be performed by a specialist or a trained practitioner in chronic GvHD grading. Female or male genital GvHD is not scored if a practitioner is unable to examine the patient.

For joint and fascia, the photographic-range and motion (P-ROM) score is an exploratory measure and is not included in the calculation of global severity.

Abnormality present but explained entirely by non-chronic GvHD documented cause must be specified and the organ will be excluded from calculation of the global severity.

Computation of the chronic GvHD global severity, as mild, moderate or severe is indicated in the table below:

Table 3. NIH global severity of chronic GvHD

Mild	1 or 2 Organs involved with no more than score 1 *plus* Lung score 0
Moderate	3 or More organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

7.1.3 Indication for systemic therapy

Symptomatic mild chronic GvHD may often be managed with local therapies alone (eg, topical corticosteroids for the skin involvement).

In contrast, in patients with moderate or severe chronic GvHD (eg chronic GvHD that involves 3 or more organs or with a score of 2 or greater in any single organ), systemic immunosuppressive therapy should be considered.

However, in some organ sites (mouth, eyes, genital tract), aggressive local therapy alone may be reasonable, as response to systemic therapy may be suboptimal or may not warrant the risk of treatment.

7.2 Pre-treatment evaluations (1 week before ATO treatment)

In addition to chronic GvHD assessment detailed above, the following evaluations must be performed within one week prior to the first ATO cycle:

- Patients' sociodemographics including data on age, gender, and contraception
- Recipient, donor and transplant characteristics
- DLI modality (if relevant)
- Evaluation of GvHD using the chronic GvHD Activity Assessment-Clinician Form A (see below and Appendix 8)
- Patient self-reported outcome using the chronic GvHD activity assessment-patient self-report (Form B) (see Appendix 9)
- History of GvHD prophylaxis : documentation of any associated treatments and topical therapy since graft for acute GvHD or progressive form of cGvHD treated by corticotherapy < 1 mg/kg/day, whenever possible given collected clinical history
- Concomitant diseases
- Physical examination, including vital signs, weight and size (see Appendix 4 to Appendix 5)
- Documentation of daily steroid dose
- Documentation of any associated treatments and topical therapy for chronic GvHD (including glucocorticoid creams, topical tacrolimus, oral beclomethasone or budesonide, topical azathioprine and ophthalmic glucocorticoids…)
- Hematology: complete blood count (CBC) with differential counts (leucocytes, neutrophils, lymphocytes, monocytes, eosinophils counts, hemoglobin, platelets)
- Serum Chemistries: creatinine, uric acid, total bilirubin, alkaline phosphatases,

LDH, total protein, albumin, SGOT (Aspartate amino-transferase, ASAT), SGPT (Alanine amino-transferase, ALAT), calcium, glycaemia

- Infectious disease surveillance: cytomegalovirus (CMV), Epstein Barr virus (EBV) and other infectious diseases (Hepatitis [hep] B surface Antigen (Ag), Hep B surface antibody if relevant)
- Immunology: quantitative immunoglobulin measurement; lymphocyte subset analysis of B cells, T cells, and auto-antibodies
- Tumor evaluation
- Quality of life questionnaire (LSS and FACT-BMT) (see Appendix 10 to Appendix 11)
- The patient must undergo an electrocardiogram (EKT) before ATO treatment with QTc measurement
- In addition, serum levels of electrolytes (potassium, magnesium) will be measured
- If appropriate, a serum pregnancy test will be performed at the study start before any administration of the study drug
- Other tests including pulmonary function (FEV1) and imagery (chest-X ray) tests will be carried out
- A cutaneous biopsy if relevant and a coagulation test with measurement of PT and APTT will be performed

7.3 Inclusion and treatment plan

7.3.1 Inclusion

If a patient fulfills the inclusion criteria of the protocol and has signed the informed consent, he will be eligible for inclusion in the study. For inclusion purposes, a specific "Registration form" will be used, and the patient will be given a unique identification number, according to standard procedures.

The consent form must be documented by obtaining the dated signature both of the patient and of the person involved in the study, conducting the consent discussion on the consent form (see Appendix 14). The patient should have an oral and written language able to perfectly understand the language of the informed consent form. The

investigator site should write in the patient file who submitted the informed consent and the date of the submission and signatures.
The consent form should be signed before any procedure related to the protocol.
A copy of the inform consent and consent form should be given to the patient before participation, the original should be kept by the investigator site.
The initial informed consent and any amendment should be reviewed and approved by the Protection of Persons Committee (CPP) before submission and signature.
The patient and his/her legally representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. This should be documented in the patient file.

Registration of patients included in the study will be performed in the PROMISE database of the European society for Blood and Marrow Transplantation (EBMT) and in the specific electronic CRF of the study.

When connecting to the electronic CRF patient and inputting criteria for inclusion/exclusion, a number will be automatically assigned to the patient. This number will serve as reference for any exchange with the Sponsor.

7.3.2 Treatment plan

7.3.2.1 Arsenic trioxide therapy

As soon as the diagnosis of chronic GvHD requiring systemic immunosuppressive therapy is confirmed, patients will receive in addition to ciclosporine A (if relevant) and corticosteroids 1 mg/kg/day, ATO 0,15 mg/kg/day over a 4 weeks period (one cycle).
The treatment plan is indicative, but it is important to respect the number of 11 perfusions per cycle. In the case of a temporary discontinuation of ATO therapy for medical or other reasons, the canceled infusions will be scheduled as soon as possible.

- Week 1: day 1 to 5
- Week 2: 3 times per week (example: day 8, 10 and 12)
- Week 3: 2 times per week (example: day 15 and 17)
- Week 4: 1 time per week (example: day 24)

ATO should be administered within 10 days of starting prednisone 1mg/kg/day.
Follow-up dates for response assessment and laboratory tests relate to the date of ATO infusion.
Patients in partial response after the 1st cycle of ATO will be eligible to receive a second cycle of ATO as consolidation therapy. A delay of 8 weeks to a maximum of 11 weeks (from the first infusion of ATO) will be observed between the two cycles of ATO therapy.

Response definition is as follows:

- Complete remission (CR) is defined as complete disappearance of any sign of chronic GvHD

- Partial remission (PR) is defined as improvement of 1 or more point on a 4 to 7-point scale or an improvement of 2 or more points on a 10 to 12-points scale in at least 1 organ or site without progression in any other organ or site. For patients with BOS, an absolute improvement in %FEV1 of 10% predicted or more (eg, 50% to 60%) is considered a PR as long as the initial % FEV1 is < 70%. Normalization (≥80%) is considered a CR.

- Progressive disease (PD) is defined as at least one organ system has worsened by at least one stage without improvement of any other organ systems from baseline:

- For skin, eye, esophagus, and upper and lower gastro-intestinal (GI) tract, a worsening of 1 point or more on the 0 to 3 scale is considered progression, except a change from 0 to 1, which is considered trivial progression since it often reflects mild, nonspecific, intermittent, self-limited symptoms and signs that do not warrant a change of therapy.
- For joint/fascia, a worsening of 1 point or more on the 0 to 3 scale is considered progression, even if from 0 to 1, because a change to score 1 was considered meaningful progression that would prompt a change in therapy. For joints assessed by the photographic range of motion, a worsening of 1 or more points for the 7-point scales and 1 or more points for the 4-point scale is considered progression.
- For mouth, a worsening of 2 or more points on the 1-point scale indicates

progression.

- Worsening of liver GvHD is defined by an increase of 2 or more times the upper limit of normal for the assay for alanine transaminase, alkaline phosphatase, or total bilirubin.
- For patients with lung involvement, absolute worsening of FEV1 by 10% pre-dicted or more (eg, 50% to 40%) is considered progression, as long as the final %FEV1 is < 65% (because initial %FEV1 must be < 75% to establish the diagnosis of lung involvement). If PFTs are not available, then worsening of the clinical lung score based on symptoms by 1 or more points should be scored as progression, except from score 0 to 1, which is considered trivial progression because of its lack of specificity for lung chronic GvHD.

- Mixed response is defined as CR or PR in at least one organ accompanied by progression in another organ

- Unchanged: outcome that do not meet criteria for CR, PR, PF or mixed response are considered unchanged

Response determination for chronic GvHD is indicated in the table below:

Table 4. Response determination for chronic GvHD

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

- Resistance is defined as lack of a CR/PR 2 weeks after the last ATO infusion,

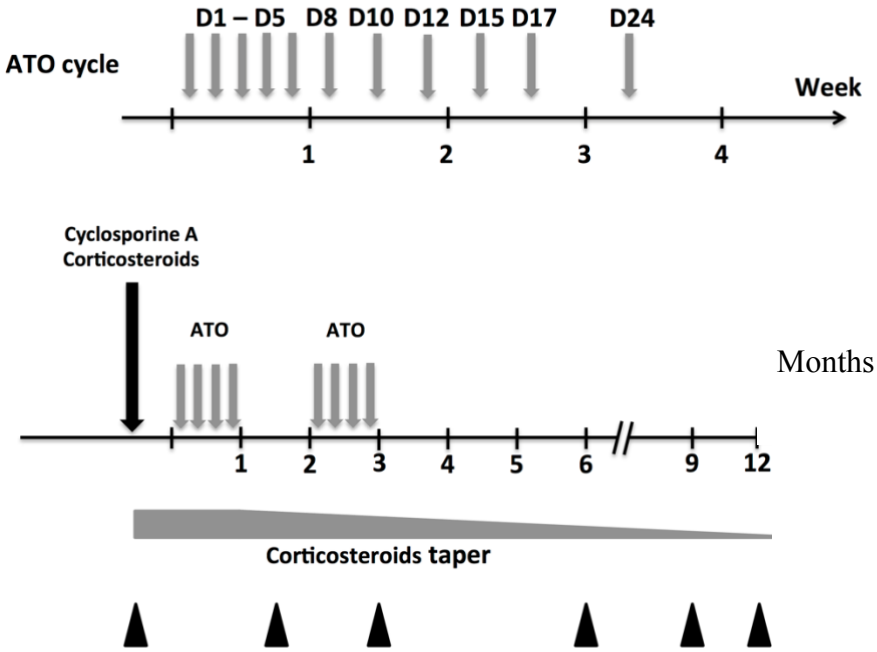
requirement for alternative therapy or death from GvHD before the last ATO infusion

- Treatment failure is defined as death, recurrent or progressive malignancy or the initiation of new systemic treatment for chronic GvHD. Increased dosing of existing treatment will not be considered as failure.

Indications for secondary systemic treatment of chronic GvHD:

Secondary systemic immunosuppressive treatment or other systemic treatment for control of chronic GvHD will be given at the discretion of the investigator in consultation with the GvHD team. In general, secondary systemic treatment is not indicated as long as there is continuing improvement in at least one manifestation of chronic GvHD and no progression of any other manifestations.

Figure 1. Study plan of investigational product and secondary systemic treatment



Dose delay, modification and reinitiation

Treatment with ATO must be interrupted, adjusted, or discontinued before the scheduled end of therapy at any time that a toxicity grade 3 or greater, on the National Cancer Institute Common Toxicity Criteria, is observed and judged to be possibly related to ATO treatment. Patients who experience such reactions that are considered ATO related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the previous daily dose. If the toxic event does not recur within 3 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.

ECG and Electrolyte Monitoring Recommendations

During therapy with ATO, potassium concentrations must be kept above 4 mEq/l and magnesium concentrations must be kept above 1.8 mg/dl. In case of increase of QTc > 500 msec (Summary of Product Characteristics (Trisenox)), syncope, rapid or irregular heartbeat development, the treatment is immediately interrupted and the patient must be hospitalized, the EKG monitored continuously, serum electrolytes assessed and a cardiological advice requested.

ATO therapy must be discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, the syncope and irregular heartbeat cease. In accordance with the Safety Committee, the treatment could be reinitiated after the validation of the posology.

8. Examinations and evaluations

8.1. Calendar of evaluations

The total length of follow up period for this protocol will be for 12 months following the first infusion of ATO, with a first follow up at 6 and 14 weeks, then at 6, 9 and 12 months post-inclusion.

In case of postponement of several administrations of Arsenic trioxide or second cycle of treatment, the visit of follow up must also be postponed to respect the 2 weeks delay after the end of the cycle (for 6 and 14 weeks only).

8.2.Evaluations during treatment with ATO

The following evaluations must be performed:

- Before each administration of ATO during the first and the second cycle (if applicable):
  - Physical examination, including vital signs
  - EKG with measurement of the QTc interval according to the formula in Section 11.8
  - Serum chemistries: calcium, potassium, magnesium, creatinine
  - Collection of whole blood (5 mL) for pharmacokinetic assessment (see Section 8.4)
- At time of treatment initiation each week (for example, days 1, 8, 15 and 24):
  - Physical examination, including vital signs, weight
  - GvHD assessment
  - Monitoring and recording of treatment associated, particular attention must be paid to drugs reported to prolong QT interval and/or induce torsade de pointes (see Appendix 7)
  - EKG with measurement of the QTc interval according to the formula in Section 11.8
  - Serum chemistries: potassium, magnesium, creatinine, uric acid, total bilirubin, alkaline phosphatases, LDH, total protein, albumin, SGOT (ASAT) and SGPT (ALAT) (twice a week), calcium, glycaemia (twice a week)
  - Hematology: complete blood count (CBC) with differential counts (twice a

week)

- Coagulation test with measurement of PT and APTT (twice a week)
- Infectious disease surveillance: CMV, EBV as per centre practice (and Hep B surface Ag, Hep B surface antibody if relevant)
- Monitoring the kinetics of certain autoantibodies [antinuclear antibody (AAN), anti-neutrophil cytoplasmic antibody (ANCA)]
- Collection of whole blood (5 mL) for pharmacokinetic assessment (see Section 8.4)
- Collect of whole blood (35 mL) for immunological evaluations ((see Section 8.3)

8.3.Surveillance post-treatment with ATO

- Participation in this study should not substantially modify the clinical and biological surveillance of this type of patients with chronic GvHD. The monitoring and evaluation timetable are outlined in the appendices.
- Clinical monitoring performed weekly during the first month of ATO therapy, then twice a month up to three months, and then on a monthly basis during six months, and then on a trimester basis at 9, 12 months (whenever possible no more than +/- 5 days before or after calculated visit date allowed):

  Note : if a second cycle needed, the corresponding follow-up visit Week 8 becomes optional because it is very close to the first visit of the second cycle (Week 9)

  - Physical examination
  - GvHD assessment
  - Documentation of daily steroid dose
  - Monitoring and recording of all adverse events (AEs) and therapeutic measures taken (medications and other significant interventions) during all the study
  - Documentation of any associated treatments and topical therapy for chronic GvHD (including glucocorticoid creams, topical tacrolimus, oral beclomethasone or budesonide, topical azathioprine and ophthalmic glucocorticoids…)
  - Documentation of disease progression or relapse

- Documentation of any introduction of new systemic therapy
- Evaluation of GvHD using the chronic GvHD Activity Assessment-Clinician Form A (see below and Appendix 8) at 6 and 14 weeks, and at 6, 9 and 12 months
- Biological monitoring performed weekly or twice weekly (according to the parameters) during the first month of ATO therapy, then twice a month up to three months, and then on a monthly basis during 6 months, and a trimester basis at 9 and 12 months
- Hematology: complete blood count (CBC) with differential counts
- Coagulation test with measurement of PT and APTT
- Serum Chemistries: potassium, magnesium, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT (ASAT), SGPT (ALAT), calcium
- Infectious disease surveillance: CMV, EBV as per centre practice (and Hep B surface Ag, Hep B surface antibody if relevant)
- Serum immunoglobulin levels will be measured at baseline entry on the study and monthly per centre practice. Repletion of intravenous immunoglobulin (IVIG) is advised for patients with recurrent infections or IgG levels <400 mg/dL
- Monitoring the kinetics of certain autoantibodies [antinuclear antibody (AAN), anti-neutrophil cytoplasmic antibody (ANCA)]

➢ Immunological evaluations:

- Given the apoptotic effects of ATO on the immune system, and as a secondary endpoint, this protocol will include some immunological evaluations at inclusion, at one, 3, 6 and 14 weeks (at 9, 10 and 12 weeks in case of second treatment cycle) and at 6 months and later at 9 and 12 months (as described in the protocol flow-chart), aiming to assess the immune effects of the drug.
- Therefore, peripheral blood samples (30 mL on heparin tubes) and serum (5 mL) at each time point will be drawn to assess allogeneic and protective antibody responses prior to and after ATO therapy : at one week (W1D1), at second and fourth week (W2D8 and W4D24), at evaluation visits 6 et 14 weeks (at 9, 10 and 12 weeks in case of second treatment cycle) and at 6 months and later at 9 and 12 months (as described in the protocol flow-

chart).,:

- To evaluate the effect of ATO on the oxidative stress pathway: Evaluation of the circulating level of ROS using the free oxygen radicals test (FORT)
- To decipher the relation between dendritic cells, in particular plasmacytoid dendritic cells, helper T cells (Th1, Th2, Th17) and follicular helper T cells and B cells in the context of chronic GvHD under treatment by ATO:

  Peripheral blood mononuclear cells (PBMC) phenotype and immunophenotype

  RNA sequencing of sorted CD4+ lymphocytes and dendritic cells to evaluate the effect of ATO on cell signaling

  Circulating level of Th1, Th2 and Th17 related cytokines
- Evaluate the effect of ATO on T cells and B cells diversity (if relevant)

  T-cell receptor (TCR) and B-cell receptor (BCR) sequencing

Immunological evaluations are centralized at Saint-Antoine Hospital (Paris, France). The whole blood samples of patients (except for patients included at Hôpital Saint-Antoine) will be shipped within 24 hours to the Hôpital Saint-Antoine, at room temperature by a carrier. The serum of patients are frozen at -80°C and should be globally sent at the end of each cycle or at the end of study by a carrier.

- Quality of life parameters:
  - Quality of life questionnaire at inclusion (LSS and FACT-BMT), at 6 and 14 weeks, and 6, 9 and 12 months (LSS and FACT-BMT) (see Appendix 10 to Appendix 11)
- Tumor response assessment:
  - These examinations will be made depending on the type of the underlying disease and according to each centre practice.

8.4. Pharmacokinetic measurement

A sample of 5 mL of whole blood on heparin tube will be taken before each administration at D2, D3, D4, D5, D8, D12, D17 and D24 of cycle 1 and cycle 2 (if

applicable). Plasma and red cells will harvested and frozen at –20°C or –80°C and should be globally carried by a professional carrier at the end of each cycle or at the end of study to the Lariboisière laboratory (Pr Poupon).

Determination of plasma and erythrocyte arsenic

Blood will be drawn on heparin tube. At arrival at the laboratory, the blood will be centrifuged and the plasma will be separated from blood cells. The arsenic dosage is determined in the plasma and red blood cells by spectrometry in inductively coupled plasma mass spectrometers (ICP-MS) on Elan DRCE (Perkin Elmer) equipped of a reaction cell. In this technique, the pre-diluted sample will be sent in aerosol form in argon plasma of which temperature is about 8,000 K. All the species present in the sample are then reduced to the state of atom, mostly in ionized form.

The ions formed are then extracted from the plasma and introduced into the reaction cell, and then, in the mass spectrometer which separates the ions according to their mass to charge ratio. At the output of the mass spectrometer, a sensor counts the number of ions given mass (Poupon J, 2008). As the arsenic contents only a mass 75 isotope (^{75}As) interfered by $^{40}Ar^{35}Cl$, oxygen will be used as the reaction gas for forming the read 91 AsO mass free of interference. Internal quality controls (Seronorm® serum levels 1 and 2, Seronorm® whole blood levels 1, 2 and 3, Sero, distributed by Ingen) will be analyzed in each series. The detection limit will be 1 nmol L (0.001 mol/L) in the serum.

After analysis, the samples will be stored at -40 ° C until the end of the study.

9. Evaluation criteria

9.1. Study endpoints

9.1.1. Primary endpoint

The primary endpoint will be the evaluation of response rate (CR and PR) of chronic GvHD at 6 months after diagnosis of chronic GvHD and treatment with ATO in combination with prednisone, with or without cyclosporine, as first line treatment.

9.1.2. Secondary endpoints

The secondary endpoints will be as follows:

- Percentage of patients with documented failure free survival (FFS), defined as death, recurrent or progressive malignancy, or the initiation of a new systemic treatment for chronic GvHD

- Corticosteroids dosage and percentage of reduction in corticosteroids dosage at 6 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment

- Cumulative incidence of transplant-related mortality (TRM) of infectious and non-infectious origin at 6 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment

- OS and PFS at 6 and 12 months after diagnosis of chronic GvHD and treatment ATO as first line treatment

- Descriptive analysis of quality of life parameters at inclusion, at 6 and 14 weeks, and at 6, 9 and 12 months after diagnosis of chronic GvHD and treatment with ATO as first line treatment

- Tolerability and safety of ATO in combination with prednisone, with or without cyclosporine, in patients with chronic GvHD after allo-SCT

9.2. Assessment of chronic GvHD

The clinical stage of chronic GvHD will be assessed in each patient at 6 weeks post-inclusion, then again at 14 weeks and 6 months, then a check-up will be performed at 9, and 12 months post-inclusion. The revised grading system proposed by the NIH (see Appendix 1) will be used (Jagasia et al., 2015). Thus the global scoring of chronic GvHD according to the NIH proposal will be performed (Lee et al., 2015). As far as is possible, a single senior physician, (or fellow with advanced and specific training), at each centre will review the organ status of all patients enrolled in this study. Therefore, for documenting chronic GvHD assessment, the investigator will complete the Chronic GvHD Activity Assessment-Clinician Form A (see Appendix 2). In addition, patients will complete the Chronic GvHD Activity Assessment-Patient self-reported Form B, the "Lee Chronic GvHD Symptom Scale" and the FACT-BMT. The Lee symptom scale was developed as a 30-item symptom scale with 7 subscales to capture the chronic GvHD-specific symptom burden. The symptom scale showed to correlate with patients self-assessed mild, moderate, and severe chronic GvHD manifestations in cross-sectional analysis. Longitudinal assessments showed that changes in overall health status correlated best with changes in quality of life as measured by the FACT-BMT. In contrast, changes in chronic GvHD severity were best detected by changes in the Lee symptom scale.

- **The NIH consensus scoring system** for individual organs is used in this study; Organ sites considered include skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, and female genital tract.

  - For skin, the composite score is split into 2 scores to document the extent of skin involvement (BSA) and the specific skin features, separately (see Appendix 6). The higher of the 2 scores is to be used for computation of global severity.

  - For eyes, scoring from 0 to 3 is based on symptoms, need for eye drops, and use of therapeutic procedure or devices.

- For lung, scoring from 0 to 3 is based on symptoms. In addition, pulmonary function tests to assess FEV1 are mandatory in this protocol. For patients with bronchiolitis obliterans, an absolute improvement in FEV1 of 10% predicted or more is considered a PR as long as the initial FEV1 is < 70%. Normalization (≥ 80%) is considered CR.

- For joint and fascia, scoring from 0 to 3 is based on symptoms. The P-ROM score is an exploratory measure that could be very useful in that exploration.

- For mouth, scoring from 0 to 12 is based on symptoms.

- For gastrointestinal tract, scoring from 0 to 3 is performed for the upper and lower gastrointestinal tract and esophagus. In addition patient weight must be recorded.

- For liver, total serum bilirubin, alkaline phosphatase and alanine aminotransferase must be recorded.

- Genital tract requires a specialist exam and measure of genital response are considered exploratory. Therefore, genital tract is not included in evaluation of chronic GvHD response.

Abnormality present but explained entirely by non-chronic GvHD documented cause must be specified and the organ will not be considered as involved for evaluation of chronic GvHD response.

In addition, physician should provide a subjective assessment of current overall chronic GvHD severity on a 4-points scale (no chronic GvHD, mild, moderate or severe) without knowledge of the calculated NIH global severity score. They should also provide an assessment of current overall chronic GvHD severity on a 11-point numerical scale (0 indicates no GvHD manifestation; 10 indicates most severe chronic GvHD symptoms possible). Clinicians should also provide their evaluations of chronic GvHD changes since the last assessment scored on a 7-point scale (very much better, moderately better, a little better, about the same, a little worse, moderately worse, very much worse). These semi-quantitative assessments may detect qualitative improvements that are clinically meaningful but not well captured using other measures.

- **Patient reported outcome**

Patient reported outcome included chronic GvHD-specific core measure with the chronic GvHD activity assessment-patient self-report (Lee Symptom Scale: LSS - Form B) and chronic GvHD non-specific ancillary measure with the FACT-BMT. Patients reported outcome are exploratory and will not be used for decision making response evaluation.

- Organ sites considered in the chronic GvHD activity assessment-patient self-report included skin and joint, mouth, genital tract and eyes. In addition, similarly to clinician assessed chronic GvHD, at each assessment, patients should score their perceptions of overall chronic GvHD severity, overall severity of symptoms, and change in symptom severity compared with the last assessment, using the same response options used by clinicians.

- For skin, patients should report their most severe itching during the past week, rated according to a 0 to 10 scale, as itching is the most frequent cutaneous symptom of chronic GvHD. These are considered recommended measures. A semi-quantitative exploratory measure, "Your skin and/or joint tightening at its worst," on a 0 to 10 scale has been added to capture severity of skin sclerosis. Informal cognitive testing suggested that including both "skin" and "joint" tightening in the question was not confusing for patients.
- For mouth, patients should report their mouth sensitivity (irritation resulting from normally tolerated spices, foods, liquids, or flavors), rated according to a 0 to 10 scale for peak severity during the past week.
- For genital tract, both female and male genital symptoms may be captured by the exploratory item rating "worst genital discomfort" on a scale from 0 to 10.
- For eyes, patients should report a "chief eye complaint" rated according to a 0 to 10 scale for peak severity during the past week. The complaint can change from visit to visit, but only 1 "chief eye complaint" is graded.

9.3. Response criteria

- Numbering of weeks/timing of events

Week 1 is the week corresponding to the first infusion of ATO. Weeks are counted from this week onwards, unless stated to the contrary. Investigators should take care not to confuse weeks post-ATO with weeks post-transplantation.

- Response to the study regimens:

- Assessment of response (CR vs. PR): The main issue in chronic GvHD is the lack of consensus criteria for the assessment of the response. In 2015 an NIH sponsored meeting was held with a panel of experts on chronic GvHD. Their proposal for grading of chronic GvHD will be used in this protocol (see Appendix 1).

- The following definitions will be used:

- Complete remission (CR) is defined as complete disappearance of any sign of chronic GvHD

- Partial remission (PR) is defined as improvement of 1 or more point on a 4 to 7-point scale or an improvement of 2 or more points on a 10 to 12-points scale in at least 1 organ or site without progression in any other organ or site. For patients with BOS, an absolute improvement in %FEV1 of 10% predicted or more (eg, 50% to 60%) is considered a PR as long as the initial % FEV1 is < 70%. Normalization (≥ 80%) is considered a CR.

- Progressive disease (PD) is defined as at least one organ system has worsened by at least one stage without improvement of any other organ systems from baseline

- For skin, eye, esophagus, and upper and lower GI tract, a worsening of 1 point or more on the 0 to 3 scale is considered progression, except a change from 0 to 1, which is considered trivial progression since it often reflects mild, nonspecific, intermittent, self-limited symptoms and signs that do not warrant a change of therapy.
- For joint/fascia, a worsening of 1 point or more on the 0 to 3 scale is considered progression, even if from 0 to 1, because a change to score 1 was considered meaningful progression that would prompt a change in therapy. For joints assessed by the photographic range of motion, a worsening of 1 or more points for the 7-point scales and 1 or more points for the 4-point scale is considered progression.

- For mouth, a worsening of 2 or more points on the 1-point scale indicates progression.
- Worsening of liver GvHD is defined by an increase of 2 or more times the upper limit of normal for the assay for alanine transaminase, alkaline phosphatase, or total bilirubin.
- For patients with lung involvement, absolute worsening of FEV1 by 10% predicted or more (eg, 50% to 40%) is considered progression, as long as the final %FEV1 is < 65% (because initial %FEV1 must be < 75% to establish the diagnosis of lung involvement). If PFTs are not available, then worsening of the clinical lung score based on symptoms by 1 or more points should be scored as progression, except from score 0 to 1, which is considered trivial progression because of its lack of specificity for lung chronic GvHD.

- Mixed response is defined as CR or PR in at least one organ accompanied by progression in another organ

- Unchanged: outcome that does not meet criteria for CR, PR, PF or mixed response are considered unchanged

- Resistance is defined as lack of a CR/PR 2 weeks after the last ATO infusion, requirement for alternative therapy or death from GvHD before the last ATO infusion

- Failure is defined as death, recurrent or progressive malignancy or the initiation of new systemic treatment for chronic GvHD increased dosing of existing treatment will not be considered as failure

9.4. Infections

These will be classified, as far as is possible, by pathogenic agent, clinical syndrome, and localization according to the definitions of the Infectious Diseases Working Party of the EBMT, available on the website of the EBMT:

https://www.ebmt.org/Contents/Research/TheWorkingParties/IDWP/Pages/Infectious-Diseases.aspx

Date of onset, duration, treatment and outcome will also be noted, as well as prophylaxis prior to infective episode.

9.5.Cause of death

When determining the cause of death, investigators should classify deaths occurring from infection and from multiple organ failure in the presence of chronic GvHD, as being caused or related to GvHD.

10. Statistical considerations

10.1. General considerations

A statistical analysis plan which describes the statistical analyses planned for the study will be written and signed before database lock.

Data will be described using qualitative and quantitative data as follows:

- Qualitative data will be described in frequency and percentage and will be represented using histograms or diagrams of distribution
- Quantitative data will be described using the calculations of average, standard deviation, median, and extreme values

10.2. Analyses data set

Every patient included in the study and who has received at least one infusion of ATO will be taken into account at time of data analysis.

Patients who do not receive any injection of ATO will not be analyzed and will be replaced to obtain 24 patients provided in the statistical analysis.

10.3. Statistical analyses

A descriptive analysis will be conducted on the following parameters:

- Patients and transplant characteristics
- Primary and secondary endpoints

The toxicities rate will be calculated and will be given with their 95% confidence intervals.

The probabilities of survival will be estimated by the Kaplan-Meier method and by calculating the cumulative incidences for relapse/progression, and non-relapse mortality incidence.

10.4. Definition of Endpoints

10.4.1. Efficacy success

Efficacy success is defined as the response rate (CR+PR) at 6 months after the first ATO infusion, with no secondary systemic therapy (defined below) at any time. Death or dropout with lack of follow-up information after response of chronic GvHD but before the final analysis is expected to occur infrequently and will not be used to negate categorization as efficacy success for purposes of this study, since the treatment had been effective in controlling chronic GvHD. It is possible that systemic immunosuppressive treatment will be discontinued before resolution of all reversible manifestations of chronic GvHD in some patients. Topical therapy may be continued in this situation, at the discretion of the managing physician. Discontinuation of immunosuppressive medications for the purpose of inducing an anti-tumor response after the development of recurrent or secondary malignancy will not be categorized as efficacy success.

It is possible that initial treatment with ATO might improve the prospects of success after secondary systemic therapy. This endpoint will not be used, however, to avoid any confounding biases.

10.4.2. Efficacy failure

Efficacy failure is defined as early treatment failure is first checked at week 6 post ATO. Treatment failure will be defined as:

- Required initiation of a new systemic treatment for chronic GvHD before week 6
- Recurrent or progressive malignancy before week 6
- Death before week 6

Failure-free survival (FFS), is defined as death, recurrent or progressive malignancy, or the initiation of a new systemic treatment for chronic GvHD (defined below).

From the perspective of the patient, secondary therapy and death have very different significance with respect to efficacy, since the need for secondary therapy does not inevitably lead to death. From the perspective of the clinical trial, however, both events indicate that the study-drug did not have the desired efficacy.

Discontinuation of treatment with study-drug because of toxicity will not be categorized as efficacy failure in and of itself, since it is possible that a short period of treatment with the study-drug could have long lasting benefit ultimately resulting in efficacy success. After a toxic study-drug outcome, patients will be followed for any subsequent initiation of secondary systemic treatment development of recurrent malignancy, death from causes other than recur- rent malignancy, or dropout with lack of follow-up information. Any of these events occurring during primary treatment for chronic GvHD will be categorized as efficacy failure.

10.4.3. Secondary systemic therapy

Secondary systemic therapy includes any intervention intended to control chronic GvHD through an immunosuppressive effect from oral or parenteral administration of any systemic medication not originally given under auspices of this protocol. Examples include, but are not limited to the following: azathioprine, rapamycin, infliximab, daclizumab, etanercept, antithymocyte globulin, thalidomide, chloroquine, clofazimine, extracorporeal photopheresis, and psoralen with UVA irradiation.

Topical therapy, including glucocorticoid creams, topical tacrolimus, oral beclomethasone or budesonide, topical azathioprine and ophthalmic glucocorticoids, is not considered as secondary systemic therapy.

An increase in the dose of prednisone and any resumption of treatment with prednisone or study-drug after previous discontinuation for any reason is not considered as secondary systemic therapy. Any increase in the dose of ciclosporine or resumption of treatment with ciclosporine after previous discontinuation for any reason is not considered as secondary systemic treatment, if the drug in question was included in the immunosuppressive regimen when treatment for chronic GvHD was started.

A change in treatment from ciclosporine to tacrolimus because of drug toxicity is not considered as secondary treatment. This information must be reported in the electronic CRF of the study.

10.4.4. Recurrent malignancy

For purposes of this study, recurrent malignancy after allo-SCT is defined as clinical or histopathologic evidence demonstrating the presence of any malignancy considered as the indication for transplant. Recurrent malignancy after allo-SCT will also be defined as any post-transplant intervention not routinely used to prevent the development of overt recurrence, prompted by laboratory evidence of persisting malignant cells but without clinical or histopathologic evidence of recurrence. Recurrent malignancy after a non- myeloablative or reduced intensity conditioning regimen will be defined as any ad hoc post- transplant intervention intended to induce a donor immune-mediated anti-neoplastic effect, prompted by clinical or laboratory evidence indicating the need to eliminate persistent or progressive malignancy. Examples of such interventions include accelerated withdrawal of systemic immunosuppressive medications and donor lymphocyte infusion.

10.5. Missing data handling

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

10.6. Early stopping rules

Experience acquired with the use of ATO in various clinical situations does not suggest a significant risk of study drug-related severe toxicities. Therefore, for the purpose of this study, no criterion for early stopping will be defined in advance.

10.7. Calculation of the number of patients

Based on results from the literature, the hypothesis for the primary endpoint is an improvement in response rate (CR and PR) at 6 months after the diagnosis of chronic GvHD and start of ATO from 60% to 85%. Using a one-step A'Hern procedure (A'Hern RP, 2001) (and anticipating a dropout rate around 10%), 24 (21+3) patients are needed. If the number of successful cases is 17 or more among the 21 patients, the hypothesis that the CR rate at 6 months is less than 60% is rejected with a target error rate of 0.05 (alpha probability). The beta probability in this case is 0.2.

11. Safety Management

11.1. Adverse Events

The following definitions and explanations are given to enable investigators and study nurses to correctly record, report and review adverse eventss (AEs) in order to comply with the safety requirements according to Good Clinical Practice (GCP) standards and the local and European requirements.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE) (see Section 11.3.3) requiring immediate notification to Sponsor. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. For AEs with a causal relationship to the investigational medicinal product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Sponsor concurs with that assessment.

11.2. Reporting Period

SAEs require immediate notification to Sponsor beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, i.e., prior to undergoing any trial-related procedure and/or receiving investigational medicinal product, through 30 days after the administration of the last dose.

Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational medicinal product is suspected.

AEs (serious and non-serious) should be recorded on the electronic CRF from the time the subject has taken at least one dose of trial treatment through last subject visit.

11.3. Definitions

11.3.1. Definition of an AE

An AE is any untoward medical occurrence in a clinical investigation subject administered an investigational medicinal product; the event do not need necessarily have a causal relationship with the treatment or usage.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug abuse;
- Drug misuse;
- Medication error;
- Drug interactions;
- Exposure in utero.

Worsening of signs and symptoms of the cGVHD should not be reported as AEs in the appropriate section of the electronic CRF. PD is defined as at least one organ system has worsened by at least one stage without improvement of any other organ systems from baseline.

11.3.2. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing *(outside of protocol-stipulated dose adjustments)* or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

11.3.3. Definition of a Serious Adverse Event

A SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization for medical reasons (e.g. prolongation of hospitalization for social reasons is excluded);
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the cGVHD (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal during the trial or within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as SAE.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

11.3.4. Hospitalization

AEs reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

11.4. Severity Assessment

Treatment related toxicities and other AE and SAE are classified according to the NCI common toxicity criteria (CTC), **specification for stem cell transplantation**, as outlined in the appendix of this protocol. The updated CTC can be downloaded from the worldwide web using the following URL:

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

Please note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

11.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational medicinal product caused or contributed to an AE.

Not Related: Where a temporal (timely) relationship of the onset of the event, relative to the administration of the investigational medicinal product is not reasonable (e.g. as crash as passenger), or where another cause can explain the occurrence of the event by itself. [*Considered as having not a reasonable possibility to be related to the investigational medicinal product*]

Unlikely: Where a temporal (timely) relationship of the onset of the event, relative to the administration of the investigational medicinal product is unlikely and or because another cause may be suspected. [*Considered as having not a reasonable possibility to be related to the investigational medicinal product*]

Possibly Related: Where a temporal (timely) relationship of the onset of the event, relative to the administration of the investigational medicinal product is reasonable, but the event could have been due to an equally likely cause. [*Considered as having a reasonable possibility to be related to the investigational medicinal product*]

Probably Related: Where a temporal (timely) relationship of the onset of the event, relative to the administration of the investigational medicinal product is reasonable and the event is more likely to be explained by the investigational medicinal product than by another cause. [*Considered as having a reasonable possibility to be related to the investigational medicinal product*]

Definitely Related: Where a temporal (timely) relationship of the onset of the event, relative to the administration of the investigational medicinal product is reasonable and there is no other cause to explain the event or a re-challenge is positive. [*Considered as having a reasonable possibility to be related to the investigational medicinal product*]

If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational medicinal product caused the event, then the event will be handled as "related to investigational medicinal product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational medicinal product", this should be clearly documented on trial records.

In addition, if the investigator determines a SAE is associated with trial procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

11.6. Exposure In Utero

For investigational medicinal products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if:

1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational medicinal product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational medicinal product (maternal exposure);
2) a male has been exposed, either due to treatment or environmental, to the investigational medicinal product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial subject or trial subject's partner becomes or is found to be pregnant during the trial subject's treatment with the investigational medicinal product, the investigator must submit this information to Sponsor on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Sponsor product in a pregnant woman using the Exposure in Utero Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Sponsor of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

"Spontaneous abortion" includes miscarriage and missed abortion.

All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medicinal product should be reported.

11.7. Reporting

11.7.1. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAE. If a SAE occurs, expedited reporting will follow local and European regulations, as appropriate.

All AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

11.7.2. Serious Adverse Event Reporting Requirements

If a SAE occurs, Sponsor is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Exposure in Utero cases.

For all serious AEs, the investigator is obligated to pursue and provide information to Sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor.

It is the investigators responsibility to maintain an accurate and up to date record of all AEs/occurrences in patients participating in the clinical trial. This record, including details of nature, onset, duration, severity, outcome and any relationship to investigational medicinal product, should be noted in the patient s medical notes. It is the investigators responsibility to review all events occurring at their site and as such the investigator must ensure that the patients are not compromised. Any appropriate action must be taken to protect the patients whilst ensuring validity of the results. It is the investigator responsibility to report correctly and on time to the sponsor SAE and to answer to queries at time.

All SAE Form must be sent to the sponsor by fax or e-mail to:

AnticipSanté

40, rue de Fontenelle – 78160 ~ Marly le roi

E-mail: **sae-medsenic@anticipsante.com**

11.7.3. Non-Serious AE Reporting Requirements

Non-serious AEs are to be reported on the AE eCRFs, which are to be submitted to Sponsor.

11.8. Frequent AEs

The most frequently reported AEs of ATO are specified in the SPC (See Appendix 12) and provided below:

The most frequent events related to ATO are those:

- Related to cardiovascular system (tachycardia, QT prolongation…)

Prolongation of the QT interval in the EKG has been observed during treatment with ATO. This can lead to ventricular tachycardia (*torsade de pointes*) with a fatal outcome. In this context, possible interaction with other drugs that prolong the QT interval must also be taken into account (see Appendix 7 for drugs reported to prolong QT interval and/or induce *torsade de pointes*).

For this reason, close monitoring of the EKG and of the electrolytes is necessary during treatment with ATO. In particular, the Mg^{++} and K^{+} levels should always be kept in the high-normal range, taking in consideration possible concomitant treatments that deplete electrolyte levels (e.g. amphotericin B, furosemide etc.). In the EKG, the QT interval is represented by the QRS complex, the ST segment and the T wave. Its measurement starts from the deepest point of Q wave to the end of T wave. This interval greatly depends on the heart rate and several formulas have been proposed to adjust the QT interval for heart rate in order to obtain the corrected QT interval (QTc); however, no one of these proposed formulas is satisfactory (Indik JH, 2006; Luo S, 2004; Sagie A, 1992). Despite that, data from medical literature indicate that one of the most simple method for adjusting the QT interval for heart rate is the Framingham formula (Indik JH, 2006; Luo S, 2004; Sagie A, 1992):

QTc=QT+0.154*(1000-RR)

Using this formula, the upper normal limits of QTc interval calculated from the EKC of 10,303 subjects collected from 4 US hospitals (Luo S, 2004) are reported in the table below:

Table 5. Upper Limits (98%,in msec) of Normal QTc for Framingham formula (Luo S, 2004)

Heart Rate (HR)	MALE (5,420)	FEMALE (4,883)	BOTH (10,303)
All HR	454	461	457
HR < 60	455	463	459
HR 60 to 99	454	462	458
HR > 99	436	434	436

For increased accuracy, the QT interval should be measured on serial EKGs and several successive beats and averaged for each EKG. The averaged QT value obtained should be used in the above formula in which all measurement must be expressed in msec (i.e.: 0,500 sec=500 msec). Applying this formula, a QTc interval > 500 msec must be considered prolonged (Summary of Product Characteristics (Trisenox)).

- Related to hepatotoxicity: increase in serum bilirubin and/or SGOT and/or SGPT and/or alkaline phosphatase,
- Related to Hematological toxicity. This drug may induce severe and prolonged myelosuppression with subsequent anemia, neutropenia, thrombocytopenia. Less frequently hyperleucocytosis or leucopenia have been reported.
- Related to general tolerance (fever, chills, fatigue, bleeding, edema…)
- Related to immunosuppression such as infectious complications (candidosis, herpes-zoster, pneumonia, bacteremia, septicemia, septic choc…),
- Related to digestive toxicity (nausea, vomiting, diarrhea...),
- Related to metabolism disorders (hyperglycemia, hypokalemia, hypomagnesaemia…),
- Renal insufficiency,
- Related to nervous system (paraesthesia, dizziness, headache…),
- Related to eye disorder (vision blurred),
- Related to cutaneous tissues (prurit, rash…),
- Related to musculoskeletal, connective tissue and bone disorders (myalgia, arthralgia, bone pain…).
- Related to pulmonary disorders (dyspnea,,,)

All AE not previously described in the Summary of Product Characteristics of TRISENOX® or in the Investigator Brochure of ARSCIMED® should be considered as unexpected AE.

11.9. Safety Committee

An independent safety committee (including experts in the field) will be established by the sponsor to assess at regular intervals the progress of the trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop the trial.

During the study, meetings of the Independent Data Monitoring Committee will be organized periodically.

11.10. Annual Safety Report

A safety report will be produced annually. The "Development International Birth Date" (DIBD) is used to determine the start of the annual period for the Annual Safety report (ASR). This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the ASR is the month and date of the DIBD. The start of the annual period for the ASR is the month and date of the DIBD. The data lock point of the ASR can be designated as the last day of the month prior to the month of the DIBD.

This report will be prepared by the sponsor according to the current ICH guideline E2F on development safety update report. Additionally, the two following listings will be provided: Interval line listings of the Serious Adverse Reactions (SARs) that were reported to the sponsor during the period covered by the ASR; and Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

This report will be submitted to the competent authorities and to the ethics committees by the sponsor within 60 days from the above anniversary date.

In addition, an independent data safety committee will be constituted to assist the sponsor (please see Section 11.9).

12. Quality Control

12.1. Good Clinical Practice

The study will be performed according to the Guidelines for Good Clinical Practice (ICH Harmonized Tripartite Guideline for Good Clinical Practice, (17.01.1997)).

The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and SPC. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A trial master file should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2. Auditing

To guarantee a high quality of treatment for the patients within the present study, the sponsor will insure that the participating centres fulfill the following criteria:

- fulfilling of legal requirements
- experience of the principle investigator of the entire study and the respective centre with respect to study conduct
- International Conference on Harmonization (ICH)/GCP knowledge and certifications

12.3. Monitoring

Regular monitoring is an essential part of the study conduct. It will be performed by the Sponsor of the study. After the initiation visit, the frequency of monitoring visits will depend on the course of the study, and recruitment. It is the monitor's responsibility to make the local investigators and all the staff who is involved into the study or the care of the patients familiar with the protocol.

During the course of the study, the monitor will control the progress of the study, the commitment to the protocol, the documentation and careful usage of the study medication, and the maintenance of GCP guidelines and legal obligations. Problems as well as changes in reported data will be worked out in collaboration with the local investigator, who is obliged to cooperate with the monitor and to allow access to the patients' charts. Source data verification is performed by the monitor. This protocol is classified as a "D" risk level estimated for the patients (Phase II= very high risk predictable).

Inclusion criteria will be verified in 100% of patients. The monitor will have to respect that the data she/he comes into contact with are highly confidential. A monitoring report will be provided for each visit.

12.4. Data management

The coding and data control for the exploitation of results of the study will be conducted by the Contract research Organization (CRO) in charge of the study, FOVEA (Rueil-Malmaison, France), according to its standard operating procedures, ICH guidelines, and under the supervision of the Sponsor.

12.4.1. Data entry

All study data will be recorded and stored in a computerized database within the CRO, under the supervision of the Data Manager and under appropriate procedures. The data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

12.4.2. Consistency checks

Procedures for control of electronic data (Data Computer Management) will be defined to ensure the validity of information gathered as part of this study. They will cover all of the data and will aim to highlight abnormalities as missing data or inconsistent data.

These controls will be fully described in a manual of Data Management and will be implemented in the e-CRF. The computerized handling of the data by the Sponsor may generate additional requests (discrepancy resolution forms) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

12.4.3. Data Coding

The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), while previous treatments will be coded using the World Health Organization (WHO) dictionary according to anatomic-therapeutic-chemical classification (ATC).

13. Ethical and Regulatory Considerations

The study will be conducted according to the European Union directive (ICH Harmonized Tripartite Guideline for Good Clinical Practice, (17.01.1997)). The study has to be conducted in compliance with the protocol, GCP and all applicable regulatory requirements:

- Helsinki declaration from1964, revised in Washington in 2002,
- GCP of the International Harmonization Conference (ICH E6, 17/07/96),
- European Directive (2001/20/CE) on the conduct of clinical trials,
- French law n° 2004-801 dated 6 August 2004,
- French bioethics law n° 2004-800 dated 6 August 2004.

Accordingly, investigating physicians have to provide direct access to study documents to monitoring, audits, institutional internal control, external authorities, and the members of the ethical committee. Written informed consent by the patient is mandatory.

The coordinating investigator and all investigators will be given an up-to-date investigator's brochure containing full details of the status of the pre-clinical and clinical knowledge of the study medication. As soon as new information is obtained, an updated version will be sup- plied or an amendment added to the existing investigator s brochure.

13.1. Regulatory Authorities Approval (CPP and ANSM)

No patient may be included in the study before the respective requirements of the national health authorities are fulfilled. The study will begin only after the positive vote of the responsible Ethics Committee (CPP) and after the approval by the appropriate national health authority (ANSM).

The protocol has to be followed strictly, protocol violations have to be documented and the reason has to be given (e.g. emergency measures). Any changes in the protocol can only be performed by the principle investigator or the protocol writing committee. Any subsequent changes will be reported or submitted for approval to the ethical committee and to local and national authorities.

13.2. Informed consent

Written informed consent is obtained by each patient before inclusion into the study (see Appendix 14). Using patient information sheets, as well as personal oral explanation by a local investigator at the patient's transplant centre, the patient will be informed of the aims and the investigational nature of the study, the exact procedures that will be done during treatment and evaluation, the possible risks and side effects, and of alternative treatment options. They will be informed as to the strict confidentiality of their patient data, but that authorized individuals other than their treating physician may review their medical records for study purposes. Further, the patient will be informed that their anonymized data will be scientifically analyzed and published. It will be emphasized that the participation is voluntary and that consent can be withdrawn by the patient at any time without explanation of the reason. The patient is allowed to refuse further participation in the protocol, whenever he/she wants. The patient's further treatment will not be influenced by this decision.

13.3. Investigators responsibilities

In collaboration and according to the Standard Operating Procedure (SOP) of the sponsor, a detailed list of delegation of responsibilities has been established. It is held by the sponsor, who is finally responsible for the correct performance of delegated responsibilities by the respective persons or institutions. A copy of this list will be delivered to the participating institutions.

The investigator of each institution undertakes to conduct the study according to the protocol which was approved by the ethics (CCP) and health authorities (ANSM). The investigator must not make any changes to the protocol without the permission of the sponsor and without the CCP has given a favorable opinion on the proposed amendments.

It is the responsibility of the investigator responsible for the study in the participating centre:

- To provide his curriculum vitae as well as co-investigators
- To identify team members, who will participate in the study and define their responsibilities
- To start recruiting patients after authorization of the sponsor
- To try to include the required number of patients within the period of recruitment

It is the responsibility of each investigator:

- To obtain the informed consent dated and signed personally by the patient before any selection process specific to the study
- To fill in an electronic case report form (e-CRF) for each patient included in the study and allow direct access to source documents to validate e-CRF data
- To correct, sign and date the correction(s) of the e-CRF for each patient enrolled
- To notify the sponsor of any SAE(s) within the time required
- To accept regular monitoring visits and possibly those of auditors mandated by the sponsor or inspectors from authorities

All documentation on the study (protocol, consents, notebooks observation, file investigator, etc.) and original documents (laboratory results, x-rays, minutes of consultations, review reports...) must be kept in a safe place and considered confidential material.

The Investigator will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in the study records.

13.4. Sponsor responsibilities

It is the responsibility of the sponsor to:

- Subscribe insurance to cover its liability for the harmful consequences of research
- Provide the investigators with all information necessary to conduct the research
- Apply for authorization from a relevant CPP
- Apply for authorization from ANSM
- Inform the Directors and Pharmacists of health facilities
- Inform ANSM of any serious incidents that may be due to research

13.5. Biocollections

Biological samples collected for the immunological assessment will be stored in a biocollection. The patient informed consent will be collected and the samples will be stored in one of the biocollections of Assistance Publique-Hôpitaux de Paris: the Hematology biobank approved by INCa and located at the Saint-Antoine Hospital (Declaration N° DC-2009-963 and authorization N° AC-2013-1992).

The Sponsor shall finance the study and endorses a policy of insurance covering the financial consequences of its civil liability in accordance with regulations in order to guarantee against possible damage resulting from the research.
Non-compliance with the Research Legal Conditions is a cause for guarantee exclusion.

13.6. Archiving

The data archiving will be under the responsibility of the investigator and, as required by law.

Data will be kept for a minimum of 15 years after the end of the study.

13.7. Final report and publications rules

At the end of the study evaluation, the principle investigator presents a final report, containing the clinical report, single tables, and the final conclusions. Publication of the results is realized independently from the outcome of the study. The study or parts of the study should be published by the writing committee only which consists of the persons in charge of the study as mentioned on the front page. According to the EBMT rules, co-authors will be offered to the local PI of participating centres, the order depending on the number of patients included by the respective centres, or depending on their contribution to the protocol or the realization of the study. Other investigators will be mentioned in the addendum. All publications and/or communications related to this study should at least mention the PI of the study and the sponsor.

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15. Appendices

Appendix 1: Signs and symptoms of cGvHD (NIH consensus criteria, Jagasia et al. Bone Marrow Transplant, 2015)

Signs and Symptoms of chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)	Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and chronic GVHD)
Skin	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures		
Females	Vaginal scarring or clitoral/labial agglutination	Ulcers		
Males	Phimosis or urethral/meatus scarring or stenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children
Liver				Total bilirubin, alkaline phosphatase > 2 × upper limit of normal ALT > 2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease‖	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

ALT indicates alanine aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

* In all cases, infection, drug effect, malignancy, or other causes must be excluded.

† Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

‡ Common refers to shared features by both acute and chronic GVHD.

§ BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).

‖ Pulmonary entities under investigation or unclassified.

¶ Diagnosis of chronic GVHD requires biopsy.

Appendix 2: Organ scoring of cGvHD
(NIH consensus criteria, Jagasia et al. Bone Marrow Transplant, 2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ **S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Figure 1. Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplemental Figure). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

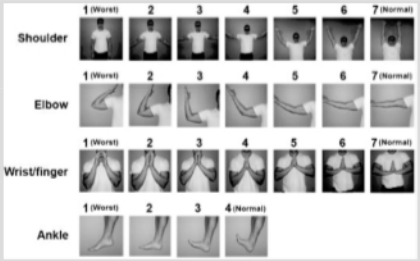
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*[†]) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs[‡] and females with or without discomfort on exam	☐ Moderate signs[‡] and may have symptoms with discomfort on exam	☐ Severe signs[‡] with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)*	❑ **No GVHD**	❑ **Mild**	❑ **Moderate**	❑ **Severe**

Photographic Range of Motion (P-ROM)



Appendix 3: Genital tract cGvHD assessment and scoring Form (NIH consensus criteria, Jagasia et al. Bone Marrow Transplant, 2015)

Name:_____ **Date of birth:** _____**Assessment date:** _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT ***Check:*** ☐ Male ☐ Female	☐ No signs	☐ Mild signs and females may have symptoms* WITH discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe signs with or without symptoms *

Currently sexually active:

☐ Yes ☐ No

Check all signs that apply:

☐ Lichen planus-like features

☐ Lichen sclerosis-like features

☐ Vaginal scarring (female)

☐ Clitoral/labial agglutination (female)

☐ Labial resorption (female)

☐ Erosions

☐ Fissures

☐ Ulcers

☐ Phimosis (male)

☐ Urethral meatus scarring/ stenosis (male)

☐ *Abnormality present but NOT thought to represent GVHD (specify cause):*_____

☐ *Abnormality thought to represent GVHD PLUS other causes(specify cause):*_____

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection*.

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:

a) Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a qtip. Vulvar pain elicited by the gentle touch of a qtip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
b) If the woman is sexually active, determine whether qtip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:
1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phymosis or urethral scarring or stenosis. Severity of signs:
1) Mild: lichen planus-like feature;
2) Moderate: lichen sclerosus-like feature or moderate erythema;
3) Severe: phimosis or urethral/meatal scarring.

Biopsy obtained: ☐ **Yes** ☐ **No** **Site biopsied:**_____**GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by (print name):_____**Date form completed:** _____

Appendix 4: Performance Status (WHO)

0 - Asymptomatic

1 - Symptomatic, fully ambulatory

2 - Symptomatic, in bed < 50 % of day

3 - Symptomatic, in bed > 50 % of day but not bedridden

4 - Bedridden

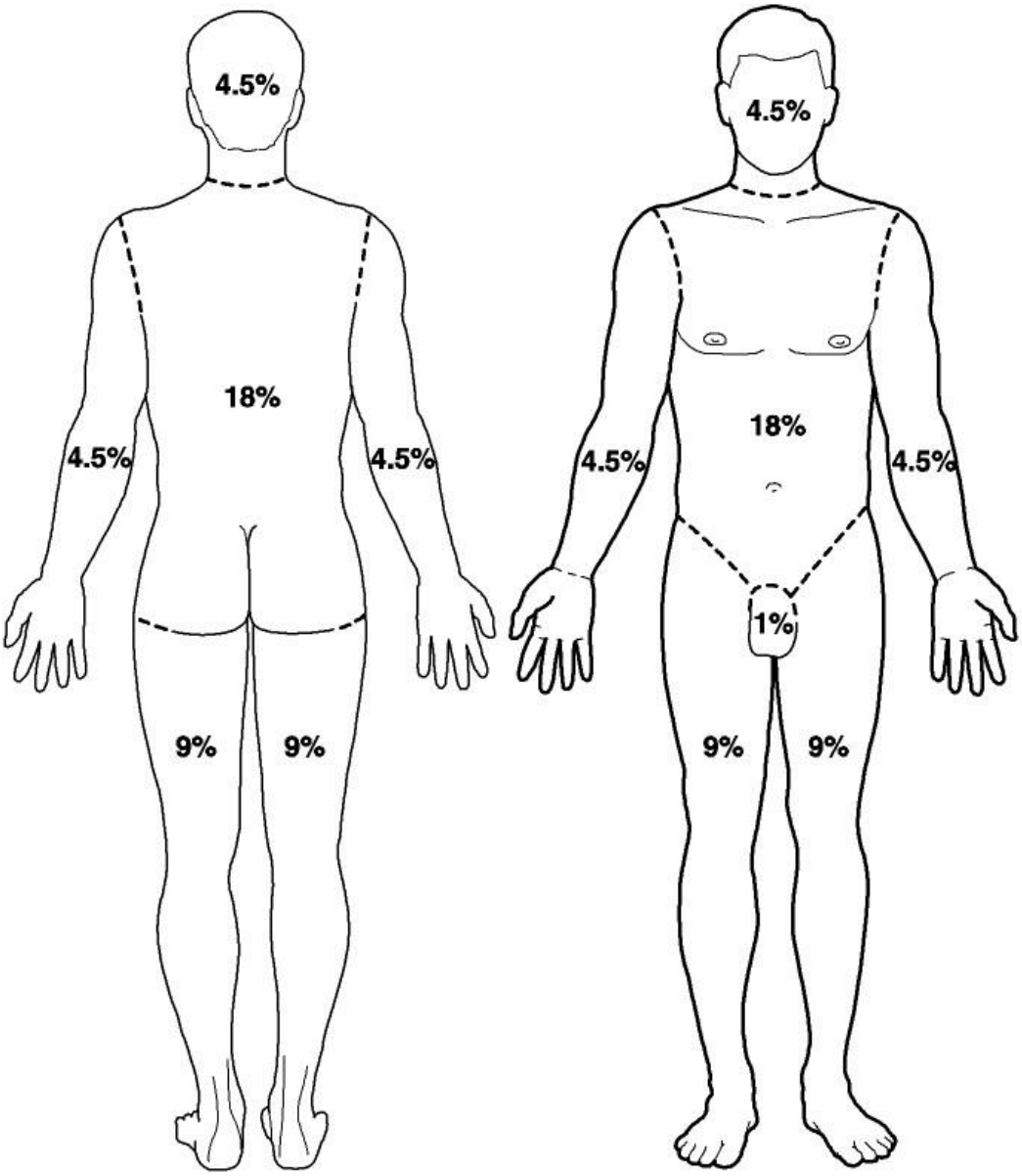
Appendix 5: Karnofsky Performance Scale Index

Able to carry on normal activity and to work; no special care needed.
100 - Normal no complaints; no evidence of disease.
90 - Able to carry on normal activity; minor signs or symptoms of disease.
80 - Normal activity with effort; some signs or symptoms of disease.

Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
70 - Cares for self; unable to carry on normal activity or to do active work.
60 - Requires occasional assistance, but is able to care for most of his personal needs.
50 - Requires considerable assistance and frequent medical care.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
40 - Disabled; requires special care and assistance.
30 - Severely disabled; hospital admission is indicated although death not imminent.
20 - Very sick; hospital admission necessary; active supportive treatment necessary.
10 - Moribund; fatal processes progressing rapidly.
0 - Dead

Appendix 6: Rule of 9s for body surface area



Appendix 7: Drugs reported to prolong QT interval and/or induce torsade de pointes
(Gowda RM et al. Torsade de pointes: the clinical considerations, Int J Cardiol, 2004)

Category	Drugs
Antiarrhythmics	Disopyramide, procainamide, n-acetyl-procainamide, quinidine, beperdil, mexiletine, propafenone, flecainide, amiodarone, bretylium, sotalol, ibutilide, dofetilide, azimilide, aprindine, ajmaline, almokalant, mibefradil, clofilium, sematilide
Antimicrobials	Erythromycin, clarithromycin, azithromycin, ampicillin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, trimethoprim-sulfamethoxazole, troleandomycin, Pentamidine, quinine, foscarnet, fluconazole, itraconazole, ketoconazole, chloroquine, halofantrine, mefloquine, amantadine, spiramycin
Antihistamines	Astemizole, diphenhydramine, terfenadine, ebastine, hydroxyzine
Antidepressants	Doxepin, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, venlafaxine, citalopram, ketanserin
Antipsychotics	Chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, felbamate, haloperidol, droperidol, mesoridazine, pimozide, quetiapine, risperidone, thioridazine, ziprasidone, lithium, chloral hydrate, pericycline,
Anticonvulsants	Felbamate, fosphenytoin
Anesthetics	Sevoflurane
Antianginal/vasodilators	Bepridil, lipoflazine, prenylamine, intracoronary papaverine
Antihypertensives	Isradipine, nicardipine, moexipril/ hydrochlorthiazide
Anticancer agents	Arsenic trioxide, tamoxifen
Antilipemic	Probucol
Antimigraine agents	Sumatriptan, zolmitriptan, naratriptan

Diuretics	Indapamide thiazide, furosemide
Endocrine	octreotide, vasopressin
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone, erythromycin
Others	Arsenic trioxide, tizanidine, tacrolimus, salmeterol, levomethadyl, pinacidil, cromakalin, aconitine, veratridine, batrachotoxin, anthopleurin A, ketanserin, vincamine, terodiline, budipine, cesium chloride, tiapride, levomethadyl acetate, cocaine, organophosphorus compounds

Appendix 8: cGvHD activity assessment Clinician Form A (Lee SJ et al. Biol Blood Marrow Transplant, 2015)

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GvHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe cGvHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms** **Most severe cGvHD** **not at all severe symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
				Total score for all mucosal changes					

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*

Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools <u>during the past week</u>* *1= occasional loose or liquid stools, on some days <u>during the past week</u>* *2=intermittent loose or liquid stools throughout the day, <u>on almost every day of the past week,</u> **<u>without requiring</u>** intervention to prevent or correct volume depletion* *3=voluminous diarrhea <u>on almost every day of the past week, **<u>requiring</u>** intervention to prevent or correct volume depletion</u>*					
Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %
	□ Abnormality present but explained entirely by non-GvHD documented cause (specify site/alternate cause):_____ □ Abnormality present but explained entirely by non-GvHD documented cause (specify site/alternate cause):_____ □ Abnormality present but explained entirely by non-GvHD documented cause (specify site/alternate cause):_____					

CHRONIC GvHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	**SCORE 1**	**SCORE 2**	**SCORE 3**
SKIN *GvHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GvHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GvHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GvHD documented cause				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	□ No symptoms	□ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	□ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	□ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
□ Abnormality present but explained entirely by non-GvHD documented cause (specify):_____				

Shoulder

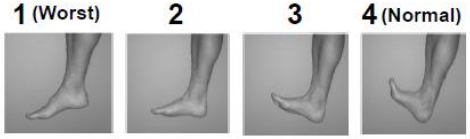
❑ Not done

Elbow

❑ Not done

Wrist/finger

Ankle



Appendix 9: cHVHD assessment patient self-report Form B
(Lee SJ et al. Biol Blood Marrow Transplant, 2015)

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GvHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.** *(SVP évaluez la sévérité des symptômes suivants au cours des sept derniers jours. SVP cochez le cercle correspondant entre 0 (symptôme non présent) à 10 (symptôme le plus sévère que vous puissiez imaginer) pour chaque élément.*	**Not You Present Imagine** *Non présent* 0	1	2	3	4	5	6	7	8	9	**As Bad As Can** *Le plus sévère que vous puissiez imaginer* 10
Your **skin itching** at its WORST? *(démangeaisons de la peau au pire moment)*	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST? *(raidissement de la peau et/ou de l'articulation au pire moment)*	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST? *(sensibilité buccale au pire moment)*	O	O	O	O	O	O	O	O	O	O	O

Your **genital discomfort** at its WORST? *(gêne au niveau génital au pire moment)* (Women – vagina, vulva, or labia) (Men – penis) (*Femmes - vagin, vulve, ou lèvres)* *(Hommes - pénis)*	O	O	O	O	O	O	O	O	O	O	O

Eyes *(Yeux)*	What is your main complaint with regard to your eyes? *(Quelle est votre principale plainte concernant vos yeux?)*	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe): *SVP cotez la sévérité de ce symptôme, de 0 (pas du tout sévère) à 10 (le plus sévère)*	0 1 2 3 4 5 6 7 8 9 10

<u>Patient Global Ratings:</u>

1. Overall, do <u>you</u> think that your chronic graft versus host disease is mild, moderate or severe? *(Dans l'ensemble, pensez-vous que votre maladie chronique du greffon contre l'hôte est légère, modérée ou sévère ?)*
1= mild *(légère)*
2=moderate *(modérée)*
3=severe *(sévère)*

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.
(SBP entourer le chiffre indiquant la gravité de vos symptômes de votre maladie chronique du greffon contre l'hôte, où 0 correspond à des symptômes de cGvHD qui ne sont pas du tout sévères et 10 aux symptômes de GvHD chronique les plus sévères).

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe
Symptômes pas du tout sévères

Most severe cGvHD symptoms possible
Symptômes les plus sévères

3. <u>Compared to a month ago</u>, overall would you say that your cGvHD symptoms are:
(Par rapport à il y a un mois, dans l'ensemble diriez-vous que vos symptômes de cGvHD sont)

+3= Very much better *(Beaucoup mieux)*
+2= Moderately better *(Modérément mieux)*
+1=A little better *(Un peu mieux)*
0= About the same *(A peu près identiques)*
-1=A little worse *(Un peu plus mauvais)*
-2=Moderately worse (*Modérément plus mauvais*)
-3=Very much worse (*Beaucoup plus mauvais*)

Appendix 10 : Lee Symptom Scale
(Lee SJ et al. Biol Blood Marrow Transplant, 2004)

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4