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

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STATISTICAL ANALYSIS PLAN

Protocol Title:	**Phase II study of first line treatment of Chronic Graft versus Host Disease with Arsenic Trioxide**
Protocol Number:	GMED16-001 Eudract number: 2016-002358-18
Compound:	ATO®
Phase:	Phase II
Sponsor:	MEDSENIC 204, avenue de Colmar F-67100 - Strasbourg
SAP Author:	Marine RAGOT-BENSEGHIR
SAP Version:	Version 3.0
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STATISTICAL ANALYSIS PLAN

DOCUMENT HISTORY

Version	Date	Author
Final v1	13/06/2018	Myriam Labopin
Final v2	08/08/2019	Maëva Dupuis-Deniaud
Final v3	21/12/2020	Marine Ragot-Benseghir

1. SIGNATURE PAGE AND APPROVALS

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Approved by Maëva DUPUIS-DENIAUD Biostatistician consultant MDSTAT	Date
Sponsor's representative Pr François RIEGER CEO – Scientific Director MEDSENIC	Date
Sponsor's representative Dominique GAIDA Clinical Project Manager MEDSENIC	Date

2. 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 cyclosporine 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 cyclosporine, in patients with chronic GvHD after allo-SCT
Study design	Prospective, national, multicentre, 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 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. 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 manifestations (total bilirubin, transaminases and alkalines phosphatases) g/ Pulmonary function evaluation

	h/ Evaluation of the musculoskeletal manifestations, especially the amplitude of 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 - 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 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 - Right bundle branch block plus left anterior hemiblock, bifascicular block - Central or peripheral neuropathy - 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 cyclosporine 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 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 irritation 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. *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 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 - 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 an 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 analysed 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: December 2020 Clinical study Report: March 2020

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALAT/SGPT	Alanine Amino-Transferase
Allo-SCT	Allogeneic Stem-Cell Transplantation
APL	Acute Promyelocytic Leukemia
ASAT/SGOT	Aspartate Amino-Transferase
ATO	Arsenic Trioxide
ATRA	All-trans Retinoic Acid (tretinoin)
CBC	Complete Blood Count
cGvHD	Chronic Graft Versus Host Disease
CMV	Cytomegalovirus
CR	Complete Remission
DLI	Donor Lymphocytes Infusion
EBV	Epstein Barr Virus
e-CRF	Electronic Case Report Form
EKG	Electrocardiogram
FACT-BMT	Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplantation subscale
FAS	Full Analysis Set
FEV	Forced Expiratory Volume
FFS	Failure-free Survival
GHVD	Graft Versus Host Disease
Hep	Hepatitis
HLA	Human Leucocyte Antigen
HY	Y-chromosome–encoded
ICH	International Conference on Harmonization
IQR	inter-quartile range
IVIG	Intravenous Immunoglobulin
HSCT	Hematopoietic Stem Cell Transplantation
LSS	Lee Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
NRM	Non-relapse Mortality
OS	Overall Survival
PDC	Plasmacytoid Dendritic Cells
PFS	Progression-free Survival
PI	Principal Investigator
PP	Per Protocol
PR	Partial Remission
RIC	Reduced Intensity Conditioning
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
TRM	Transplant-related Mortality
WHO	World Health Organization

5. ETHICS

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 from 1964, 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 supplied or an amendment added to the existing investigator s brochure.

5.1 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.

5.2 INFORMED CONSENT

Written informed consent is obtained by each patient before inclusion into the study. Using patient information sheets, as well as personal oral explanation by a local investigator at the patient's transplant 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.

5.3 INVESTIGATORS RESPONSABILITIES

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.

5.4 SPONSOR RESPONSABILITIES

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

5.5 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 ^{O} DC-2009-963 and authorization N ^{O} 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.

5.6 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.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor	**MEDSENIC** 204, avenue de Colmar F-67100 Strasbourg Tel: + 33 (0) 1 79 25 14 42
CEO- Scientific Director	**Pr François Rieger** Mail:
Executive Director	**Véronique Pomi** Mail:
Clinical Project Leader	**Dominique Gaïda, PhD** Mail:
Coordinating Investigator	**Pr Mohamad MOHTY** Service d'Hématologie Clinique Hôpital Saint Antoine AP-HP F-75012 – Paris Tel:
Contract Reasearch Organization	PopsiCube – Fovea 6 rue Jean-Pierre Timbaud Le Campus – Bât A1 Sud F-78180 Montigny le Bretonneux Tel: Fax:

7. INTRODUCTION

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). Chronic GvHD (cGvHD) is the cause of death in up to one third of all long-term survivors after transplantation for leukemia and is consistently associated with decreased quality of life, impaired functional status, ongoing need for immunosuppressive medications and infectious complications. Standard first line systemic treatment for cGvHD is orally administered corticosteroids (prednisolone 1 mg/Kg/d) and cyclosporine, with a median duration reported between 18 and 23 months. Therapy with corticosteroids is often unrewarding and the toxicities from prolonged corticosteroid administration are great. Chronic GvHD emerges from alloreactive processes between donor-derived immune cells and host cell populations. While its pathophysiology is still poorly understood, data in humans support a role of both T and B cells in a highly complex network. How these T- and B-cell networks interact has not been resolved.

Arsenic derivatives have been identified as compounds with therapeutic potential for over 2000 years in Greek and Chinese medicine. 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 acute promyelocytic leukemia (APL). The use of ATO has also been explored in many other hematologic malignancies and in solid tumors. Its role has also been explored in murine models of autoimmune and autoinflammatory diseases. 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. In a murine model of chronic GvHD, ATO effect was mediated through the depletion of glutathione and the overproduction of H2O2 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 triggers B cells death in a phenomenon which cooperates for controlling chronic GvHD.

This leads to the hypothesis that ATO delivered during the course of the disease or even early at diagnosis of chronic GvHD- and possibly in prevention of cGvHD before its detection- will be an effective treatment. To test this hypothesis, we proposed this study of ATO in combination with corticosteroids as first line therapy for newly diagnosed chronic GvHD after allo-SCT. We hypothesized that the addition of ATO to prednisone for the initial treatment of chronic GvHD will increase the overall response rate and enable a more rapid and effective corticosteroids taper. We authorized the use of cyclosporine A, as a somewhat widely adopted measure, due to its use for its supposed possible beneficial action on acute GvHD in the early weeks after allografting and sometimes continuously maintained in spite of recognized inefficacy to influence the course of the autoimmune processes going on under the designation of cGvHD.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 OBJECTIVES

8.1.1 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 Ciclosporin as first line treatment.
The aim of this study is to assess whether ATO allows improving response rate at 6 months after the diagnosis of chronic GVHD from 60% (historical rate) to 85%.

8.1.2 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 Ciclosporin, in patients with chronic GvHD after allo-SCT.

8.2 ENDPOINTS

8.2.1 Primary endpoint

The primary endpoint is the evaluation of response rate (CR and PR) at 6 months after the first ATO infusion, with no secondary systemic therapy at any time before M6.
NIH grade of chronic GVHD will be used for the exact definition of this endpoint.

- 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-points 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.

- More details for response determination are given in the following table:

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.

8.2.2 Secondary endpoints

- OS is defined as the time from first infusion of ATO to death, regardless of the cause
- FFS is defined as related death, progression, or initiation of a new systemic treatment for chronic GvHD
- PFS is defined as survival with no evidence of relapse or progression of the original disease

- 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
- Quality of life parameters using FACT-BMT and Lee Symptom Scale scores at 6 and 14 weeks, 6, 9 and 12 months after first infusion of ATO
- Tolerability and safety of ATO

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

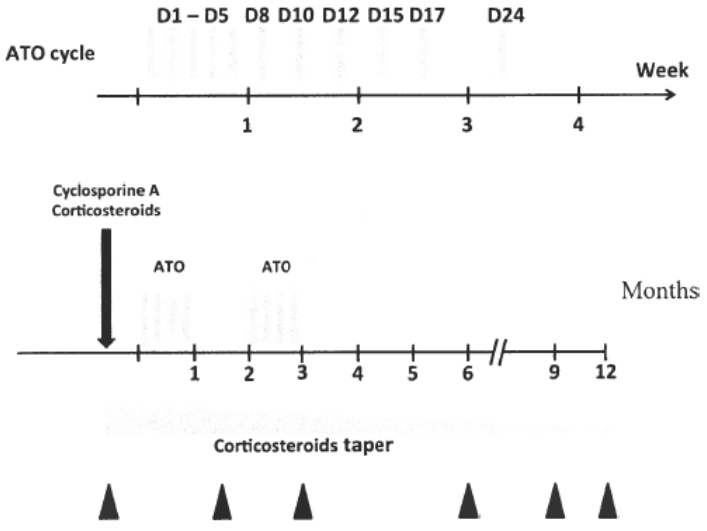
The study GMED16-001 is a prospective, national, multicenter, non-randomized phase II study that will include a total number of 24 patients.

The duration of participation panned 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®.

9.2 SELECTION OF STUDY POPULATION

9.2.1 Inclusion criteria

Patients 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.
- 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
- 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

9.2.2 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
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
- Central or peripheral neuropathy
- 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

9.3 TREATMENTS

9.3.1 Treatments administered

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.

9.3.2 Identity of Investigational Product(s)

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

9.3.3 Administration

- 0, 15 mg/kg/infusion on days I 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 Ciclosporin 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 I mg/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 1 1 weeks (from the first infusion of ATO) will be observed between the two cycles of ATO therapy.

9.3.4 Method of Assigning Patients to Treatments Groups

Not Applicable

9.3.5 Blinding

Not Applicable

9.3.6 Prior and Concomitant Therapy

9.3.6.1 Ciclosporin A

- Ciclosporin A will be delivered using local standard criteria, (if relevant).
  However:
  - Ciclosporin level should lie within the therapeutic range (i.e. 200-400 ng/mL): to harmonize CSA target levels
  - Ciclosporin-induced renal insufficiency should lead to dose adjustment and even temporary withdrawal of the drug

- Suggested guidelines for initial dose of Ciclosporin A:

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

- Monitoring of Ciclosporin level:
  - Concentrations ofCiclosporin in the plasma may be monitored at the discretion of the investigator. Dose adjustments may be made to maintain Ciclosporin 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 Ciclosporin.
  - Medications that could increase the concentration of Ciclosporin include diltiazem, nicardipine, verapamil, metoclopramide, ketoconazole, fluconazole, itraconazole, erythromycin and methylprednisolone.
  - Medications that could decrease the concentration of Ciclosporin include rifampycin, phenytoin, phenobarbital and carbamazepine.

- Deviations from guidelines for administration of Ciclosporin
  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 Ciclosporin may require dose adjustments, which should be managed according to individual transplant centre practice.

9.3.6.2 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:

Prednisone Taper Schedule

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.

9.3.6.3 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 I 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 CMVseropositive 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.

9.3.6.4 Prohibited concomitant treatments

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

9.4 EFFICACY AND SAFETY VARIABLES

9.4.1 Efficacy and Safety Measurements Assessed and Schedule of Assessments

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

	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 – QTc1 measurement	*	*1	*			
Hematology3	*	*9	*	*	*	*
Biochemistry4	*	*2/9	*	*	*	*
Coagulation test5	*	*9	*	*	*	*
Infectious disease surveillance	*	*2		*	*	*
Serum immunoglobulin level	*			*	*	*
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.

9.5 DATA QUALITY ASSURANCE

9.5.1 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.

9.5.2 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

9.5.3 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 11= 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.

9.5.4 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 (RueilMalmaison, France), according to its standard operating procedures, ICH guidelines, and under the supervision of the Sponsor.

9.5.4.1 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.

9.5.4.2 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.

9.5.4.3 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).

12.4 STATISTICAL ANALYSIS METHODES PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

12.4.3 Statistical and Analytical Plans

12.4.3.1 General approaches

All continuous data will be summarized using the following statistics: n (non-missing sample size), mean, standard deviation, median, minimum (min) and maximum (max). All categorical/qualitative data will be presented using the frequency and the percentage of patients who are in the particular category. In general, all data will be listed, sorted by site, subject, and by visit number within subject. All summary tables will be annotated with the total population size relevant to that table/treatment, including any missing observation.

The mean and the standard deviation will be reported to one decimal place greater than the original data. Median, minimum and maximum will use the same number of decimal places as the original data. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”.

Type 1 error rate will be set at 0.05.

All statistical analyses will be conducted using SAS version 9.4.

12.4.3.2 Handling of Dropouts or Missing Data

Every effort will be made to keep the number of missing values for all parameters to a minimum. The number of missing values will be reported together with summary statistics for each variable.
Missing data on overall survival is assumed to be null as patient care after transplantation is very close. Any patient prematurely withdrawn or ending the study without the event of interest (progression, death) will be censored at his/her last information date.
Concerning the main endpoint (response at M6), the missing assessments will be fully discussed during the data review. The most plausible outcome (the clinically more relevant) will be used for the main analysis. Other methods of imputation (for example, worst

outcome: missing data=failure) could be used for sensitivity purpose, according to the final number of missing assessments.

12.4.3.3 Interim Analyses

No interim analysis is planned.

12.4.3.4 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.

12.4.3.5 Determination of sample size

The aim of this study is to assess whether ATO allows improving response rate at 6 months after the diagnosis of chronic GVHD from 60% to 85%.

For the sample size calculation in this trial, an A'Hern one stage design has been used (ref 1).

- Let P0 be the smallest response rate, if true, implies that the role of ATO is too low and therefore the present schedule does not warrant further investigation. In the present trial, P0 has been taken as 60%.
- Let P1 be the highest response rate which, if true, implies that the feasibility is sufficiently high and therefore the current schedule warrants further investigation in clinical trials. In the present trial, P1 has been taken as 85%;
- Let α be the accepted probability of recommending for further investigation a regimen with a true discontinuation rate at least equal to P0. In the present trial, α has been taken as 0.05.
- Let β be the accepted probability of rejecting for further investigation a regimen with a true discontinuation rate less than P1. In the present trial, β has been taken as 0.20.

The required number of eligible patients is 21. To compensate for a dropout of 10%, 24 patients are planned to be included.

12.5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Any changes to the analyses described in the protocol or in approved versions of this plan will be fully documented in a specific part of the clinical study report of the study.

10. PATIENTS

10.1 DISPOSITION OF PATIENTS

All patients screened and receiving at least one infusion of ATO will be accounted for.

Derivation

Derived variables	Definition
Study completed	Yes, if the patient is present in the study at M12 No, if the patient is not present in the study at M12

The following table will be then presented:

	Analysis set (N=XX)
Study completed	n/N (XX.XX%)
Withdrawal of informed consent	n/N (XX.XX%)
Lost to follow-up	n/N (XX.XX%)
Occurrence of AE/SAE requiring premature discontinuation	n/N (XX.XX%)
Inclusion criteria not met requiring premature discontinuation	n/N (XX.XX%)
Other reason	n/N (XX.XX%)

10.2 PROTOCOL DEVIATIONS

Protocol deviations will be summarized as follows:

	Analysis set (N=XX)	
	Number of patients	**Number of deviations**
No deviation	n/N (XX.XX%)	n
Major deviation	n/N (XX.XX%)	n

11. EFFICACY EVALUATION

11.1 ANALYSES POPULATIONS

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.

The number of patients included who did not receive any infusion of ATO will be reported as well as the reason for not receiving ATO.

The following analyses populations will be considered:

- The safety population consists of all patients included in the study for whom there is any evidence that they used at least one ATO injection.

- The Full Analysis Set (FAS) population consists of included subjects who completed their first cycle of ATO and for whom the response at Week 6 after diagnosis of chronic GvHD has been evaluated.

- The Per Protocol (PP) population will exclude FAS patients with any major protocol deviations that may impact the efficacy analysis. The exclusion of patients from the PP population will be determined during the final data review meeting. Reason(s) for exclusion will be documented for each patient.

The following table will be presented:

	Analysis set (N=XX)
Safety Population	n/N (XX.XX%)
Full Set Analysis Population	n/N (XX.XX%)
Per Protocol Population	n/N (XX.XX%)

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

11.2.1 Demographic characteristics

Derivation

Derived variable	Definition
Age at inclusion (in years)	Year of inclusion – Year of birth

The following table will be presented:

Variable	Statistics / Modality	Safety Population (N = XX)
Gender	Male Female Missing	n/N (XX.X%) n/N (XX.X%) n
Age at inclusion (in years)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Contraception	Yes No Missing	n/N (XX.X%) n/N (XX.X%) n
Weight (kg)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Height (cm)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Cardiac frequency (beats/min)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Systolic arterial pressure (mmHg)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Diastolic arterial pressure (mmHg)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Temperature (°C)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
O2 saturation (%)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

11.2.2 Baseline characteristics

Derivation

Derived variable	**Definition**
Time from transplant to chronic GVHD (in days)	Assessment date - Date of the first allogeneic stem cell transplantation +1
Daily steroid dose (Prednisone): mg/kg/d	Considering the treatment line when the baseline occurs, the daily dose is calculated as: Dose*frequency/weight The frequency can be: once a day, twice a day, 1 day on 2 etc.
Daily cyclosporine dose	Considering the treatment line when the baseline occurs, the daily dose is calculated as: Dose*frequency The frequency can be: once a day, twice a day, 1 day on 2 etc.

The following table will be presented:

Variable	Statistics / Modality	Safety Population (N = XX)
Significant current disease	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Donor / Recipient features	Modality 1	n/N (XX.X%)
	Modality 2	n/N (XX.X%)
	…	…
	Modality n	n/N (XX.X%)
	Missing	n
Conditioning regimen		
Conditioning regimen	Modality 1	n/N (XX.X%)
	Modality 2	n/N (XX.X%)
	…	…
	Modality n	n/N (XX.X%)
	Missing	n
Previous infusion of DLI		
DLI	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Time from transplant to GVHD		
Time from transplant to chronic GVHD (in days)	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
Concomitant disease		
Current disease?	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Haematology		
Leucocytes	N (N Missing)	XX (XX)
	Mean ± SD	X.XX ± X.XX
	Median [Min ; Max]	X.X [X.X ; X.X]
Neutrophils	N (N Missing)	XX (XX)
	Mean ± SD	X.XX ± X.XX
	Median [Min ; Max]	X.X [X.X ; X.X]
Lymphocytes	N (N Missing)	XX (XX)
	Mean ± SD	X.XX ± X.XX
	Median [Min ; Max]	X.X [X.X ; X.X]

Monocytes	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.XX ± X.XX X.X [X.X ; X.X]
Eosinophils	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.XX ± X.XX X.X [X.X ; X.X]
Hemoglobin	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.XX ± XX.XX XX.X [XX.X ; XX.X]
Platelets	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
aPTT	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Serum chemistries		
Creatinine	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.XX ± XX.XX XX.X [XX.X ; XX.X]
Uric acid	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
Total bilirubin	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.XX ± XX.XX XX.X [XX.X ; XX.X]
Alkaline phosphatases	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
LDH	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
Total protein	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Albumin	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.XX ± XX.XX XX.X [XX.X ; XX.X]
SGOT	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]

SGPT	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
Calcium	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.XXX ± X.XXX X.XX [X.XX ; X.XX]
Glycaemia	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.XX ± X.XX X.X [X.X ; X.X]
Infectious disease surveillance		
CMV	Negative Positive Missing	n/N (XX.X%) n/N (XX.X%) n
EBV	Negative Positive Missing	n/N (XX.X%) n/N (XX.X%) n
Hepatitis B	Negative Positive Missing	n/N (XX.X%) n/N (XX.X%) n
Immunology		
Gammaglobulin level	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.XX ± XX.XX XX.X [XX.X ; XX.X]
Antinuclear antibody	Negative Positive Missing	n/N (XX.X%) n/N (XX.X%) n
ANCA	Negative Positive Missing	n/N (XX.X%) n/N (XX.X%) n
Cardiac assessment		
EKG – Performed?	Not realized Realized Missing	n/N (XX.X%) n/N (XX.X%) n
EKG – Result	Abnormal Normal Missing	n/N (XX.X%) n/N (XX.X%) n
QTc	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XXX.X ± XXX.X XXX [XXX ; XXX]
Serum levels of electrolytes		
Potassium	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.XX ± X.XX X.X [X.X ; X.X]
Magnesium	N (N Missing)	XX (XX)

	Mean ± SD	X.XXX ± X.XXX
	Median [Min ; Max]	X.XX [X.XX ; X.XX]
Results of other tests		
Performance status	0	n/N (XX.X%)
	1	n/N (XX.X%)
	2	n/N (XX.X%)
	3	n/N (XX.X%)
	4	n/N (XX.X%)
	Missing	n
Karnofsky index	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
Chest X ray	Not realized	n/N (XX.X%)
	Realized	n/N (XX.X%)
	Missing	n
If realized, chest X ray result	Abnormal	n/N (XX.X%)
	Normal	n/N (XX.X%)
	Missing	n
Cutaneous biopsy	Not realized	n/N (XX.X%)
	Realized	n/N (XX.X%)
	Missing	n
If realized, cutaneous biopsy result	Abnormal	n/N (XX.X%)
	Normal	n/N (XX.X%)
	Missing	n
% FEV1	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
Concomitant treatment		
Any concomitant treatments administrated?	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Daily steroid dose (Prednisone) mg/kg/d	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
Daily cyclosporine dose	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]

11.2.3 Signs and symptoms of cGvHD at baseline

Derivation

Derived variable	Definition
Liver score	The liver score is defined as a combination of Total bilirubin, ALT (SGPT) and AP (ALK) as follows: Score 0: Normal total bilirubin and ALT < 3 ULN and AP < 3 ULN Score 1: Normal total bilirubin with ALT ≥ 3 to 5 ULN or AP ≥ 3 to 5 ULN Score 2: Elevated total bilirubin (> 1 ULN) but ≤ 3 mg/dL or ALT ≥ 5 ULN or AP ≥ 5 ULN Score 3: Elevated total bilirubin > 3 mg/dL Missing if at least one missing serum chemistry
Involved sites number	Number of sites or organs with a score ≥ 1 at baseline (V1)

The following table will be presented:

Variable	Statistics / Modality	Safety Population (N = XX)
NIH scoring of cGVHD		
Scoring of chronic GVHD (NIH criteria)	Score 0: Asymptomatic and fully active (ECOG 0, KPS or LPS 100%)	n/N (XX.X%)
	Score 1: Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90 %)	n/N (XX.X%)
	Score 2: Symptomatic ambulatory, capable of selfcare,	n/N (XX.X%)

	> 50 % of walking hours out of bed (ECOG 2, KPS or LPS 60-70 %)	
	Score 3: Symptomatic, limited self-care > 50 % of waking hours in bed (ECOG 3-4, KPS or LPS < 60 %)	n/N (XX.X%)
	Missing	n
Skin – Abnormalities present but explained entirely by non-GvHD documented cause	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Skin score	Score 0: No BSA involved	n/N (XX.X%)
	Score 1: 1-18% BSA	n/N (XX.X%)
	Score 2: 19-50% BSA	n/N (XX.X%)
	Score 3: > 50% BSA	n/N (XX.X%)
	Missing	n
Mouth – Abnormalities present but explained entirely by non-GvHD documented cause	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Mouth score	Score 0: No symptoms	n/N (XX.X%)
	Score 1: Mild symptoms with disease signs but not limiting oral intake significantly	n/N (XX.X%)
	Score 2: Moderate symptoms with disease signs with partial limitation or oral intake	n/N (XX.X%)
	Score 3: Severe symptoms with disease signs on examination with major limitation or oral intake	n/N (XX.X%)
	Missing	n

Lung – Abnormalities present but explained entirely by non-GvHD documented cause	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Lung score + FEV1	Score 0: No symptoms	n/N (XX.X%)
	Score 1: Mild symptoms (shortness of breath after climbing one flight of steps)	n/N (XX.X%)
	Score 2: Moderate symptoms (shortness of breath after walking on flat ground)	n/N (XX.X%)
	Score 3: Severe symptoms (shortness of breath at rest: requiring 0)	n/N (XX.X%)
	Missing	n
Eyes – Abnormalities present but explained entirely by non-GvHD documented cause	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Eyes score	Score 0: No symptoms	n/N (XX.X%)
	Score 1: Mild dry eye symptoms not affecting ADL	n/N (XX.X%)
	Score 2: Moderate dry eye symptoms partially affecting ADL without new vision impairment due to KCS	n/N (XX.X%)
	Score 3: Severe eye symptoms significantly affecting ADL or unable to work because of ocular symptoms of loss or vision due to KCS	n/N (XX.X%)
	Missing	n
Gastro-intestinal – Abnormalities present but	No	n/N (XX.X%)
	Yes	n/N (XX.X%)

explained entirely by non-GvHD documented cause	Missing	n
Gastro-intestinal score	Score 0: No symptoms	n/N (XX.X%)
	Score 1: Symptoms without significant weight loss (< 5 %)	n/N (XX.X%)
	Score 2: Symptoms associated with mild to moderate weight loss (5-15 %) OR moderate diarrhea without significant interference with daily living	n/N (XX.X%)
	Score 3: 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	n/N (XX.X%)
	Missing	n
Liver – Abnormalities present but explained entirely by non-GvHD documented cause	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n
Liver score	Score 0: Normal total bilirubin and ALT or AP < 3 ULN	n/N (XX.X%)
	Score 1: Normal total bilirubin with ALT ≥ 3 to 5 ULN and AP ≥ 3 to 5 ULN	n/N (XX.X%)
	Score 2: Elevated total bilirubin (> 1 ULN) but ≤ 3 mg/dL or ALT ≥ 5 ULN or AP ≥ 5 ULN	n/N (XX.X%)
	Score 3: Elevated total bilirubin > 3 mg/dL	n/N (XX.X%)
	Missing	n
Joint and fascia – Abnormalities present but	No	n/N (XX.X%)

explained entirely by non-GvHD documented cause	Yes	n/N (XX.X%)
	Missing	n
Joints and fascia score	Score 0: No symptoms	n/N (XX.X%)
	Score 1: Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	n/N (XX.X%)
	Score 2: Tightness of rams and legs OR joints contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	n/N (XX.X%)
	Score 3: Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc...)	n/N (XX.X%)
	Missing	n
Involved sites number		
Involved sites number	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) X.X ± X.X X [X ; X]
Current patient weight		
Current patient weight (in kg)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Performance score		
Performance status	KPS ECOG LPS Missing	n/N (XX.X%) n/N (XX.X%) n/N (XX.X%) n
If ECOG	ECOG 1 ECOG 2 ECOG 3 Missing	n/N (XX.X%) n/N (XX.X%) n/N (XX.X%) n
Chronic GVHD activity assessment - Clinician		
Overall GvHD severity	No GVHD Mild	n/N (XX.X%) n/N (XX.X%)

	Moderate	n/N (XX.X%)
	Severe	n/N (XX.X%)
	Missing	n
Assessment of cGVHD severity (from 0 to 10)	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
Chronic GVHD activity assessment - Patient		
Assessment of cGVHD severity (from 0 to 10)	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]

11.3 ATO AND ASSOCIATED TREATMENTS

11.3.1 Arsenic trioxide therapy

Derivation

Derived variables	Definition
Time from diagnosis of cGvHD to first infusion of ATO (in days) *The same derivation will be applied for each ATO infusion*	Date of Cycle 1 onset – GvHD assessment date + 1 Missing if one of the two dates is missing
Time from starting Prednisone to first infusion of ATO (in days)	Date of Cycle 1 onset – Date of Prednisone onset +1 Missing if one of the two dates is missing
Number of cycles	1, if a date of cycle 1 onset is known 2, if a date of cycle 2 onset is known Missing otherwise
Total dose during Wi *Calculated at Wi={W1, W2, W3, W4} of each cycle*	For the considered period (Wi), sum of each dose took Example: C1_D1+C1_D2+C1_D3+C1_D5 for the first week
Daily dose during Wi *Calculated at Wi={W1, W2, W3, W4} of each cycle*	For the considered week, the daily dose will be calculated as follows: Total dose / Number of days with intake treatment during Wi
Time from the first infusion of ATO to the first day of the second cycle (in days)	Date of Cycle 2 onset – Date of Cycle 1 +1 Missing if one of the two dates is missing
Temporary discontinuation of ATO	Yes, if at least one missing infusion during the cycle 1 or cycle 2 if initiated

	No, if the patient has received all the planned doses

The following table will be presented:

Variable	Statistics / Modality	Safety Population (N = XX)
Time from diagnosis of cGvHD to first infusion of ATO (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Time from diagnosis of cGvHD to second infusion of ATO (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
…	…	…
Time from diagnosis of cGvHD to last infusion of ATO (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Time from starting Prednisone to first infusion of ATO (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of cycles	1 2 Missing	n/N (XX.X%) n/N (XX.X%) n
First cycle		
Number of infusions	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of weeks	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 1		
Daily dose during W1	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W1	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W1	N (N Missing) Mean ± SD	XX (XX) XX.X ± XX.X

	Median [Min ; Max]	XX [XX ; XX]
Week 2		
Daily dose during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 3		
Daily dose during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 4		
Daily dose during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Temporary discontinuation of ATO*	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
Second cycle		
Patients who entered into the 2nd cycle	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
Time from the first infusion of ATO to the first day of the second cycle (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of infusions	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Week 1		
Daily dose during W1	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W1	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W1	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 2		
Daily dose during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W2	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 3		
Daily dose during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W3	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Week 4		
Daily dose during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of days during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Total dose during W4	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Temporary discontinuation of ATO	No Yes Missing	n/N (XX.XX%) n/N (XX.XX%) n

In case of temporary discontinuation of ATO, a listing will be provided.

11.3.2 Associated treatment

- **Prednisone and Ciclosporin A**

Derivation

Derived variables	Definition
Time from diagnosis of cGvHD to Prednisone onset (in days)	Date of Prednisone onset – GvHD assessment date +1 Missing if one of the two dates is missing
Time from diagnosis of cGvHD to Ciclosporin onset (in days)	Date of Ciclosporin onset – GvHD assessment date +1 Missing if one of the two dates is missing
Treatment duration (in days) *Calculated for Prednisone and Ciclosporin*	Last treatment line end date – First treatment line start date +1 Missing if one of the two dates is missing
Daily dose for Prednisone and Ciclosporin *Calculated for Prednisone (mg/kg/d) and Ciclosporin (mg/d) separately*	First, for each treatment line, the total dose will be calculated as follows: dose*frequency*number of days The frequency can be: once a day, twice a day, 1 day on 2 etc. The average daily dose is then defined as follows: Sum of each dose treatment line / Treatment duration
Reason of change	As the treatment of a same patient can be changed several times, if a reason of change is met more than once, it will only be counted as one reason. Thus, the denominator will be the same as the analysis population (i.e. Safety Population)

Secondary immunosuppressive treatment after first ATO infusion	No, if no treatment intake Yes, if at least one treatment intake

The following table will be presented:

Variable	Statistics / Modality	Safety Population (N = XX)
Prednisone		
Time from diagnosis of cGvHD to first Prednisone dose (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Treatment duration (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Daily dose (mg/kg/d)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of changes	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Reason of change	Reason 1 Reason 2 … Reason n	n/N (XX.X%) n/N (XX.X%) … n/N (XX.X%)
Ciclosporin		
Ciclosporin intake	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
Time from diagnosis of cGvHD to first Ciclosporin dose (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Treatment duration (in days)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Daily dose (mg/d)	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Number of changes	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Reason of change	Reason 1	n/N (XX.X%)
	Reason 2	n/N (XX.X%)
	…	…
	Reason n	n/N (XX.X%)

- **Concomitant treatments**

Concomitant treatments will be presenting by descending sort of use.

The following table will be presented:

	Safety Population (N=XX)
Patients who received at least one concomitant treatment	**n/N (XX.X%)**
TRT 1	n/N (XX.X%)
TRT 2	n/N (XX.X%)
…	…
TRT n	n/N (XX.X%)

- **Secondary immunosuppressive treatment**

Variable	**Statistics / Modality**	**Safety Population (N = XX)**
Secondary immunosuppressive treatment	No	n/N (XX.X%)
	Yes	n/N (XX.X%)
	Missing	n

11.4 EFFICACY ANALYSIS

11.4.1 Primary Endpoint analysis

11.4.1.1 Response at 6 months – Main analysis

- **Complete or Partial response at 6 months (PI response)**

The proportion of response at 6 months (CR or PR) will be estimated and presented with its 95% exact (Clopper-Pearson) confidence interval. The null hypothesis H0: P ≤ P0 will be rejected in favor of the alternative hypothesis H1: P ≥ P1 if the lower bound of the 95% CI is lower than 60%.

Derivation

Derived variables	Definition
Complete or partial response	Yes, if the PI judged the patient in complete or partial response at M6 No otherwise

The following table will be presented:

Variable	Modality	FAS Population (N = XX)
Response at M6	Complete or partial response	n/N (XX.X%) [95% CI]

- **Complete and Partial response at 6 months (PI response)**

Proportion of CR and PR at 6 months will also be estimated separately, and presented with their 95% exact (Clopper-Pearson) confidence intervals.

The following table will be presented:

Variable	Modality	FAS Population (N = XX)
Response at M6	Complete response	n/N (XX.X%) [95% CI]
	Partial response	n/N (XX.X%) [95% CI]

Responses and their 95% CI will be graphically represented using a forest plot.

Furthermore, previous analyses will be performed considering the following subgroups:

- By sex
- By center
- By number of cycles of ATO (1 or 2)
- By use of Ciclosporin or not
- By number of organs involved in cGvHD
- By GvHD severity at baseline

11.4.1.2 Response at 6 months – Sensitivity analyses

a) The analysis presented in §11.4.1.1 will be performed on PP population
b) The analysis presented in §11.4.1.1 will be performed on the response at 6 months computed by Soladis.
c) The analysis presented in §11.4.1.1 will be performed on the response at 6 months based on the PI response, but excluding patients 06-07, 06-08 and 06-09.
d) The analysis presented in §11.4.1.1 will be performed on the response at 6 months computed by Soladis, but excluding patients 06-07, 06-08 and 06-09.

11.4.2 Secondary Endpoint analyses

11.4.2.1 Response by organ

The proportion of response at 6 months (Complete, partial or progressive) will be estimated and presented for each organ. No response is evaluated for an organ when no abnormalities is present at V1, except progressive disease.

Derivation

Derived variables	Definition
Complete response for each organ	Cf Appendix 1 "Evaluation de la réponse – 19OCT2020"
Partial response for each organ	
Progressive disease	
Organ not involved at any moment	

The following table will be presented:

Organ	Response at M6	FAS Population (N = XX)
Organ 1	Complete response	n/N (XX.X%)
	Partial response	n/N (XX.X%)
	Progressive disease	n/N (XX.X%)
	Organ not involved at any moment	n/N (XX.X%)

This table will be completed for skin, mouth, lung, eyes, gastro-intestinal, liver and joint & fascia.

11.4.2.2 Survival analyses

a) Failure free survival

A survival analysis will be conducted to describe the occurrence of failure between the first infusion of ATO and Vi, with Vi={M6;M12}.

Derivation

Derived variables	Definition
Failure at Vi *Calculated at Vi={M6;M12}*	Defined as death, recurrent or progressive malignancy, or the initiation of a new systemic treatment for chronic GvHD. Systemic treatment are: Methotrexate, Rapamune, TLI, Extracorporeal photopheresis, Rituximab, Jakavi, Glivec, Prograf, Imurel or other medications specified into the CRF (Vi_RESP_FAIL and or Vi_RESP_FAIL_S)
Time calculation from first ATO infusion to failure at Vi *Calculated at Vi={M6;M12}*	If the event appears: the difference of date between the first ATO infusion and the first failure (expressed in months) is calculated. The event will be not censured. (Date of first ATO infusion – Date of first failure)/30.5 If the event does not appear, the difference of date between the first ATO infusion and Vi (expressed in months) is calculated. The event will be censured.

The following table will be presented at M6:

		FAS Population (N = XX)
First time of failure between first ATO infusion and M6 (in months)	n/M (%) of events	n/N (XX.XX%)
	n/M (%) of censored	n/N (XX.XX%)

The Kaplan-Meier survival estimates will be plotted with the number of subjects at risk and 95% confidence limits.

These analyses will be also presented at M12.

b) Progression free survival

A survival analysis will be conducted to describe the occurrence of progression between the first infusion of ATO and Vi, with Vi={M6;M12}.

Derivation

Derived variables	Definition
Progressive disease at Vi *Calculated at Vi={M6;M12}*	Global progressive disease as define in Appendix 17.1
Time calculation from first ATO infusion to failure at Vi *Calculated at Vi={M6;M12}*	If the event appears: the difference of date between the first ATO infusion and the first progression (expressed in months) is calculated. The event will be not censured. (Date of first ATO infusion – Date of first progression)/30.5 If the event does not appear, the difference of date between the first ATO infusion and Vi (expressed in months) is calculated. The event will be censured.

The following table will be presented at M6:

		FAS Population **(N = XX)**
First time of progression between first ATO infusion and M6 (in months)	n/M (%) of events	n/N (XX.XX%)
	n/M (%) of censored	n/N (XX.XX%)

The Kaplan-Meier survival estimates will be plotted with the number of subjects at risk and 95% confidence limits.

These analyses will be also presented at M12.

c) Overall survival

A survival analysis will be conducted to describe the occurrence of death between the first infusion of ATO and Vi, with Vi={M6;M12}.

Derivation

Derived variables	Definition
Death at Vi *Calculated at Vi={M6;M12}*	Yes, if the death occurs between the first ATO infusion and Vi
Time calculation from first ATO infusion to death at Vi *Calculated at Vi={M6;M12}*	If the event appears: the difference of date between the first ATO infusion and the date of death (expressed in months) is calculated. The event will be not censured. (Date of first ATO infusion – Date of death)/30.5 If the event does not appear, the difference of date between the first ATO infusion and Vi (expressed in months) is calculated. The event will be censured.

The following table will be presented at M6:

		FAS Population **(N = XX)**
Death between first ATO infusion and M6 (in months)	n/M (%) of events	n/N (XX.XX%)
	n/M (%) of censored	n/N (XX.XX%)

The Kaplan-Meier survival estimates will be plotted with the number of subjects at risk and 95% confidence limits.

These analyses will be also presented at M12.

11.4.2.3 Treatment by Corticosteroids

Derivation

Derived variables	Definition
Selection of Prednisone treatment line at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	For each visit of interest, the Prednisone treatment line selected will be the one as: Prednisone onset date ≤ Vi ≤ Prednisone end date If the visit matches with the Prednisone onset date, then the previous line is selected. If the visit matches with the Prednisone end date, then the current line is selected. If the visit cannot match with any treatment line then a missing value will be considered for this visit.
Daily dose for Prednisone at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	For each visit, the daily dose is calculated as: dose*frequency/weight The frequency can be: once a day, twice a day, 1 day on 2 etc. Then the following categories will be created: ≤ 0.25 mg/kg/d 0.26 – 0.50 mg/kg/d 0.51 – 0.75 mg/kg/d 0.71 – 1 mg/kg/d
Change from baseline at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	Decreased, if dose category at Vi < dose category at baseline Unchanged, if dose category at Vi = dose category at baseline Increased, if dose category at Vi > dose category at basleine

	If the Prednisone treatment is not started at baseline then the date of first ATO infusion will be considered.

The following table will be then presented:

Visit	Variable	Statistics	FAS Population (N=XX)
W6	Daily dose for Prednisone	≤ 0.25 mg/kg/d	n/N (XX.XX%)
		0.26 – 0.50 mg/kg/d	n/N (XX.XX%)
		0.51 – 0.75 mg/kg/d	n/N (XX.XX%)
		0.71 – 1 mg/kg/d	n/N (XX.XX%)
		Missing	n
	Change from baseline	Decreased	n/N (XX.XX%)
		Unchanged	n/N (XX.XX%)
		Increased	n/N (XX.XX%)
		Missing	n
W14	Daily dose for Prednisone	≤ 0.25 mg/kg/d	n/N (XX.XX%)
		0.26 – 0.50 mg/kg/d	n/N (XX.XX%)
		0.51 – 0.75 mg/kg/d	n/N (XX.XX%)
		0.71 – 1 mg/kg/d	n/N (XX.XX%)
		Missing	n
	Change from baseline	Decreased	n/N (XX.XX%)
		Unchanged	n/N (XX.XX%)
		Increased	n/N (XX.XX%)
		Missing	n
M6	Daily dose for Prednisone	≤ 0.25 mg/kg/d	n/N (XX.XX%)
		0.26 – 0.50 mg/kg/d	n/N (XX.XX%)
		0.51 – 0.75 mg/kg/d	n/N (XX.XX%)
		0.71 – 1 mg/kg/d	n/N (XX.XX%)
		Missing	n
	Change from baseline	Decreased	n/N (XX.XX%)
		Unchanged	n/N (XX.XX%)
		Increased	n/N (XX.XX%)
		Missing	n
M9	Daily dose for Prednisone	≤ 0.25 mg/kg/d	n/N (XX.XX%)
		0.26 – 0.50 mg/kg/d	n/N (XX.XX%)
		0.51 – 0.75 mg/kg/d	n/N (XX.XX%)
		0.71 – 1 mg/kg/d	n/N (XX.XX%)
		Missing	n
	Change from baseline	Decreased	n/N (XX.XX%)
		Unchanged	n/N (XX.XX%)
		Increased	n/N (XX.XX%)

		Missing	n
M12	Daily dose for Prednisone	≤ 0.25 mg/kg/d	n/N (XX.XX%)
		0.26 – 0.50 mg/kg/d	n/N (XX.XX%)
		0.51 – 0.75 mg/kg/d	n/N (XX.XX%)
		0.71 – 1 mg/kg/d	n/N (XX.XX%)
		Missing	n
	Change from baseline	Decreased	n/N (XX.XX%)
		Unchanged	n/N (XX.XX%)
		Increased	n/N (XX.XX%)
		Missing	n

The daily dose for Prednisone over time and the change from baseline will be graphically represented by stacked bars.

11.4.2.4 Quality of life assessment

- **FACT-BMT**

Derivation

Derived variables	Definition
Physical well-being subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	7 * (Sum of the items GP1 to GP7) / Number of items answered Missing if no item answered
Social/family well-being subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	7 * (Sum of the items GS1 to GS7) / Number of items answered Missing if no item answered
Emotional well-being subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	6 * (Sum of the items GE1 to GE6) / Number of items answered Missing if no item answered
Functionnal well-being subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	7 * (Sum of the items GF1 to GF7) / Number of items answered Missing if no item answered
BMT subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	10 * (Sum of BMT1 to BMT4 + Sum of C6 to C7 + Sum of BMT5 to BMT6 + BL4 + BMT8) / Number of items answered Missing if no item answered
Global FACT-BMT score at Vi *Calculated for Vi = {Baseine, W6, W14, M6, M9, M12}*	The global FACT-BMT score is defined as the sum of all the subscores. Missing if at least one subscore is missing
Subscale score - Change from baseline at Vi *Calculated for Vi = {W6, W14, M6, M9, M12} and for physical well-*	Subscale score at Vi – Subscale score at baseline Missing if the subscore is missing at Vi and/or baseline

being, family/social well-being, emotional well-being, functional well-being and other concerns subscores	
Global FACT-BMT scale score - Change from baseline at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	Global FACT-BMT score at Vi – Global FACT-BMT score at baseline Missing if the global FACT-BMT is missing at Vi and/or baseline

The following table will be presented:

Variable	Visit	Statistics / Modality	FAS Population (N = XX)
First subscore	Baseline	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	W6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	W14	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M9	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M12	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
First subscore – Change from baseline	W6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]

W14	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
M6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
M9	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
M12	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]

This table will be completed for:

- Physical well-being subscore
- Social/family well-being subscore
- Emotional well-being subscore Eating and digestion subscore
- Functionnal subscore
- BMT subscore
- FACT-BMT score

Global score and each subscore over time will be graphically represented by boxplots.

The change from baseline over time of the global score and each subscore will be graphically represented by the mean and its associated CI 95%.

- **Lee Symptom Scale**

Derivation

Derived variables	**Definition**
Skin subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4” Items: Abnormal skin color, Rashes, Thickened skin, Sores on skin and Itchy skin

	Missing otherwise
Eyes and mouth subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4” Items: Dry eyes, Need to use eyedrops frequently, Difficulty seeing clearly, Need to avoid certain foods due to mouth pain, Ulcers in mouth and Receiving nutrition from an intravenous line and feeding tube Missing otherwise
Breathing subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4” Items: Frequent cough, Colored sputum, Shortness of breath with exercise, Shortness of breath at rest and Need to use oxygen Missing otherwise
Eating and digestion subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4” Items: Difficulty swallowing solid foods, Difficulty swallowing liquids, Vomiting and Weight loss Missing otherwise
Muscles and joints subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4” Items: Joint and muscle aches, Limited joint movement, Muscle cramps and Weak muscles Missing otherwise

Energy subscore at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a "0" and "100" means that all answered items were a "4" Items: Loss of energy, Need to sleep more/take naps and Fevers Missing otherwise
Mental and emotional subscore at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	If at least 2 of the following items are answered, Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a "0" and "100" means that all answered items were a "4" Items: Depression, Anxiety and Difficulty sleeping Missing otherwise
Global Lee symptom scale score at Vi *Calculated for Vi = {Baseline, W6, W14, M6, M9, M12}*	The global score is defined as the average of subscores, if at least 4 are available. Missing otherwise
Subscale score - Change from baseline at Vi *Calculated for Vi = {W6, W14, M6, M9, M12} and for skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, mental and emotional subscores*	Subscale score at Vi – Subscale score at baseline Missing if the subscore is missing at Vi and/or baseline
Global Lee symptom scale score - Change from baseline at Vi *Calculated for Vi = {W6, W14, M6, M9, M12}*	Global Lee score at Vi – Global Lee score at baseline Missing if the global Lee score is missing at Vi and/or baseline

The following table will be presented:

Variable	Visit	Statistics / Modality	FAS Population (N = XX)
First subscore	Baseline	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	W6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	W14	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M9	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M12	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
First subscore – Change from baseline	W6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	W14	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M6	N (N Missing) Mean ± SD Median [Min ; Max] CI 95%	XX (XX) XX.X ± XX.X XX [XX ; XX] [XX.X ; XX.X]
	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

	CI 95%	[XX.X ; XX.X]
M12	N (N Missing)	XX (XX)
	Mean ± SD	XX.X ± XX.X
	Median [Min ; Max]	XX [XX ; XX]
	CI 95%	[XX.X ; XX.X]

This table will be completed for:

- Skin subscore
- Eyes and mouth subscore
- Breathing subscore
- Eating and digestion subscore
- Energy subscore
- Mental and emotional subscore
- Global Lee symptom scale score

Global score and each subscore over time will be graphically represented by boxplots.

The change from baseline over time of the global score and each subscore will be graphically represented by the mean and its associated CI 95%.

11.4.2.5 Assessment of chronic GvHD activity post-ATO treatment

Chronic GvHD activity (global and by organ) will be reported at 6 weeks, 14 weeks, 6, 9 and 12 months after the first infusion of ATO.

- **<u>Global chronic GvHD activity</u>**

Variable	Modality	FAS Population (N = XX)
Health care provider global ratings		
W6	None	n/N (XX.XX%)
	Mild	n/N (XX.XX%)
	Moderate	n/N (XX.XX%)
	Severe	n/N (XX.XX%)
	Missing	n
W14	None	n/N (XX.XX%)
	Mild	n/N (XX.XX%)
	Moderate	n/N (XX.XX%)
	Severe	n/N (XX.XX%)

	Missing	n
M6	None	n/N (XX.XX%)
	Mild	n/N (XX.XX%)
	Moderate	n/N (XX.XX%)
	Severe	n/N (XX.XX%)
	Missing	n
M9	None	n/N (XX.XX%)
	Mild	n/N (XX.XX%)
	Moderate	n/N (XX.XX%)
	Severe	n/N (XX.XX%)
	Missing	n
M12	None	n/N (XX.XX%)
	Mild	n/N (XX.XX%)
	Moderate	n/N (XX.XX%)
	Severe	n/N (XX.XX%)
	Missing	n

Stacked bar graphs will be used for illustrating the percentage of patients in each score category at each time points (6 weeks, 14 weeks, 6, 9 and 12 months after the first infusion of ATO).

- **Chronic GvHD activity for each organ**
  - ***Derivation***

Derived variables	**Definition**
Mouth score	For each visit of interest, sum of the 3 following scores: - Erythema (MOUTH1) - Lichenoid (MOUTH2) - Ulcers (MOUTH3) Missing if at least one missing score Score to be calculated for the following visits: W6, W14, M6, M9 and M12

The following table will be presented:

Organ score	Visit	Statistics / Modality	FAS Population (N=XX)
Organ – Abnormalities present but explained entirely by non-GvHD documented cause	W6	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Categorical score	W6	Modality 1	n/N (XX.XX%)
		…	…
		Modality n	n/N (XX.XX%)
		Missing	n
Organ – Abnormalities present but explained entirely by non-GvHD documented cause	W14	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Categorical score	W14	Modality 1	n/N (XX.XX%)
		…	…
		Modality n	n/N (XX.XX%)
		Missing	n
Organ – Abnormalities present but explained entirely by non-GvHD documented cause	M6	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Categorical score	M6	Modality 1	n/N (XX.XX%)
		…	…
		Modality n	n/N (XX.XX%)
		Missing	n
Organ – Abnormalities present but explained entirely	M9	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n

by non-GvHD documented cause			
Categorical score	M9	Modality 1 … Modality n Missing	n/N (XX.XX%) … n/N (XX.XX%) n
Organ – Abnormalities present but explained entirely by non-GvHD documented cause	M12	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
Categorical score	M12	Modality 1 … Modality n Missing	n/N (XX.XX%) … n/N (XX.XX%) n
Liver – Abnormalities present but explained entirely by non-GvHD documented cause	W6	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
Total bilirubin*	W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
SGPT*	W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
ALK*	W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Lung – Abnormalities present but explained entirely by non-GvHD documented cause	W6	No Yes Missing	n/N (XX.X%) n/N (XX.X%) n
FEV1**	W6	N (N Missing) Mean ± SD	XX (XX) XX.X ± XX.X

		Median [Min ; Max]	XX [XX ; XX]
Liver – Abnormalities present but explained entirely by non-GvHD documented cause	W14	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Total bilirubin*	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
SGPT*	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
ALK*	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Lung – Abnormalities present but explained entirely by non-GvHD documented cause	W14	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
FEV1**	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Liver – Abnormalities present but explained entirely by non-GvHD documented cause	M6	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Total bilirubin*	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
SGPT*	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
ALK*	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Lung – Abnormalities present but explained entirely by non-GvHD documented cause	M6	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
FEV1**	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Liver – Abnormalities present but explained entirely by non-GvHD documented cause	M9	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Total bilirubin*	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
SGPT*	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
ALK*	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Lung – Abnormalities present but explained entirely by non-GvHD documented cause	M9	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
FEV1**	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Liver – Abnormalities present but explained entirely by non-GvHD documented cause	M12	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
Total bilirubin*	M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
SGPT*	M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
ALK*	M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
Lung – Abnormalities present but explained entirely by non-GvHD documented cause	M12	No	n/N (XX.X%)
		Yes	n/N (XX.X%)
		Missing	n
FEV1**	M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

* Chemistry associated to liver, ** Linked to lung function

This table will be completed for the following scores:

Organ	Score
Skin	Score 0: No BSA involved Score 1: 1-18% BSA Score 2: 19-50% BSA Score 3: > 50% BSA
Skin features score	Score 0: No sclerotic features Score 2: Superficial sclerotic features “not hidebound” (able to pinch) Score 3: Deep sclerotic features, “Hidebound” (unable to pinch), Impaired mobility, Ulceration
Mouth - Erythema	None Mild erythema or moderate erythema (<25%) Moderate (>=25%) or severe erythema (<25%) Severe erythema (>= 25%)
Mouth - Lichenoid	None Lichen-like changes (<25%) Lichen-like changes (25-50%) Lichen-like changes (>50%)
Mouth - Ulcers	None Ulcers involving (<=20%) Severe ulcerations (>20%)
Eyes	Score 0: No symptoms Score 1: Mild dry eye symptoms not affecting ADL Score 2: Moderate dry eye symptoms partially affecting ADL without new vision impairment due to KCS Score 3: Severe eye symptoms significantly affecting ADL or unable to work because of ocular symptoms of loss or vision due to KCS
Gastro-intestinal (Esophageal)	0 = No esophageal symptoms

	1 = Occasional dysphagia or odynophagia with solid foods 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
Gastro-intestinal (Upper)	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
Gastro-intestinal (Lower)	0 = No loose or liquid stools during the past week 1 = Occasional loose or liquid stools, on some days during the past week 2 = Intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion 3 = Voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion
Joint and fascia	Score 0: No symptoms

	Score 1: Mild tightness of arms or legs, normal or mild decreased range of motion and not affecting ADL Score 2: Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL Score 3 : Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
Lungs	Score 0: No symptoms Score 1: Mild symptoms (shortness or breath after climbing one flight of steps) Score 2: Moderate symptoms (shortness of breath after walking on flat ground) Score 3: Severe symptoms (shortness of breath at rest, requiring O2)

This table will be also presented on PP population.

Stacked bar graphs will be used for illustrating the percentage of patients in each score category at each time points (6 weeks, 14 weeks, 6, 9 and 12 months after the first infusion of ATO).

Continuous indicators will be represented by boxplots.

- **<u>Physician assessment of current overall chronic GvHD severity</u>**

Variable	Statistics	FAS Population (N = XX)
Chronic GVHD severity from 0 (not at all) to 10 (the most severe)		
W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
W14	N (N Missing) Mean ± SD	XX (XX) XX.X ± XX.X

	Median [Min ; Max]	XX [XX ; XX]
M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Physician evaluations of current overall chronic GvHD severity over time will be graphically represented by boxplots.

- **Physician evaluations of chronic GvHD changes**

Variable	Statistics	FAS Population (N = XX)
Over the time would you say that this patient's GVHD is…		
W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

Physician evaluations of chronic GvHD changes over time will be graphically represented by boxplots.

12. SAFETY EVALUATION

12.1 ADVERSE EVENTS

All treatment related toxicities and other AE and SAE occurring from the time of signed informed consent until the end of the study are recorded. They are coded using the Medical Dictionary for Regulatory Activities (MedDRA) and classified according to the NCI common toxicity criteria (CTC), specification for stem cell transplantation.

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.

The investigator will decide whether the serious adverse event is related to trial medication. The decision will be recorded on the serious adverse event report.
The assessment of causality is made by the investigator as not related, unlikely, possibly related or definitely related.

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.

When calculating the incidence of AEs and SAEs, each subject will only be counted once and any repetitions of AEs will be ignored; the denominator will be the total population size.

Type of AE	Safety Population (N=XX)	N AEs
AE	n/N (XX.X%)	n
Serious AE	n/N (XX.X%)	n
AE leading to death	n/N (XX.X%)	n
AE leading to withdrawal	n/N (XX.X%)	n
Related AE	n/N (XX.X%)	n

Adverse events will be also presented by SOC and PT:

SOC	PT	Safety Population (N=XX)	N AEs
SOC 1	PT 1	n/N (XX.X%)	n
	PT 2	n/N (XX.X%)	n
	…	…	…
…			
SOC n	PT 1	n/N (XX.X%)	n
	PT 2	n/N (XX.X%)	n
	…	…	…

This table will be presented for each type of AE.

A list of all AEs will be produced in a table including the following items:

- Patient number
- Age at inclusion
- AE names
- AE grade
- Seriousness
- Date of onset first cycle ATO
- Date of end first cycle ATO
- Second cycle ATO (yes/no)
- Date of onset second cycle ATO
- Date of end second cycle ATO

- Relation (causality)
- Action taken for AE
- Date of onset of AE
- Outcome of AE (Resolved without sequelae/ ongoing/ death)

12.2 LABORATORY PARAMETERS

Each laboratory parameter will be described at baseline, W6, W14, M6, M9 and M12 and presented as follows:

Variable	Visit	Statistics / Modality	Safety Population (N = XX)
Laboratory parameter 1	Baseline	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
		Not clinically significant Clinically significant Missing	n/N (XX.X%) n/N (XX.X%) n
	W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
		Not clinically significant Clinically significant Missing	n/N (XX.X%) n/N (XX.X%) n
	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
		Not clinically significant Clinically significant Missing	n/N (XX.X%) n/N (XX.X%) n
	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
		Not clinically significant Clinically significant Missing	n/N (XX.X%) n/N (XX.X%) n
	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

		Not clinically significant	n/N (XX.X%)
		Clinically significant	n/N (XX.X%)
		Missing	n
	M12	N (N Missing)	XX (XX)
		Mean ± SD	XX.X ± XX.X
		Median [Min ; Max]	XX [XX ; XX]
		Not clinically significant	n/N (XX.X%)
		Clinically significant	n/N (XX.X%)
		Missing	n

…

This table will be completed for the following parameters:

- Leucocytes
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Hemoglobin
- Platelets
- PR
- aPTT
- Glycaemia
- Creatinine
- Uric acid
- Calcium
- Potassium
- Magnesium
- Total protein

- Albumin
- Total bilirubin
- Alkaline phosphatases
- SGOT (ASAT)
- SGPT (ALAT)
- LDH

12.3 PHYSICAL EXAMINATION

Each body system of the clinical examination will be described at baseline, W6, W14, M6, M9 and M12 and presented as follows:

Variable	Visit	Statistics	Safety Population (N = XX)
Parameter 1	Baseline	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
	W6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
	W14	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
	M6	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
	M9	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]
	M12	N (N Missing) Mean ± SD Median [Min ; Max]	XX (XX) XX.X ± XX.X XX [XX ; XX]

…

This table will be completed for the following parameters:

- Cardiac frequency
- Systolic arterial pressure
- Diastolic arterial pressure
- Temperature
- O2 saturation

13. DISCUSSION AND OVERALL CONCLUSIONS

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. REFERENCE LIST

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17. APPENDICES

17.1 RESPONSE CALCULATION ALGORITHM

Etude GMED_16_001 : Evaluation des réponses complètes et partielles – 19/10/2020

Les réponses sont définies comme (règles de calcul basées sur le protocole et l'article Lee et al)

- Complete response at a visit: Lorsque tous les scores de « cGVDH activity assessment form A » des organes suivants sont à 0 ou que la variable "abnormalities present but explained entirely by non-GVHD documented cause » soit égale à Oui.

Détails :

Si une valeur est manquante pour un des organes atteints lors de la visite V1, la réponse ne peut pas être considérée comme complète. le fait que la valeur est manquante sera documentée.

Si une valeur à la visite d'intérêt est manquante sur un organe non atteint lors de la visite V1, la réponse complète peut être établie, car les réponses complètes ou partielles ne sont établies que sur les organes atteints à V1.

Si « abnormalities present but explained entirely by non-GVHD documented cause » = Oui pour un organe à la visite considérée, le score de cet organe n'est pas corrigé et cet organe n'est pas considéré pour l'évaluation de la réponse complète. cela ne créera pas de valeur manquante pour cet organe et n'empêchera pas la réponse d'être considérée comme complète si les informations sur les autres organes sont disponibles.

- BSA=0 ET skin features=0
M6_GVHD_A_S (préfixe M6 ou C1W6, W14, M9 et M12 selon la visite considérée)
M6_GVHD_A_S_F_S
M6_GVHD_A_S_ABN

- Eyes=0
M6_GVHD_A_E
M6_GVHD_A_E_ABN

- Gastrointestinal=0 (pour chacun des 3 scores : Gastro-oesophageal, Gastro-upper, Gastro-lower)
M6_GVHD_A_GASTRO1
M6_GVHD_A_GASTRO2
M6_GVHD_A_GASTRO3
M6_GVHD_GAST_ABN

- Mouth=0 (considérer la somme des 3 scores : Eythema, Lichenoid, Ulcers)

```
M6_GVHD_A_MOUTH1
M6_GVHD_A_MOUTH2
M6_GVHD_A_MOUTH3
M6_GVHD_MTH_ABN
```

Joint and fascia =0

```
M6_GVHD_A_J
M6_GVHD_A_J_ABN
```

Liver : les 3 valeurs (Bilirubine, ALAT et PAL) sont en dessous des ULN (Unité limite supérieure) si le score hépatique était >0 à V1 (table 1 et annexe du protocole)

```
.<M6_GVHD_A_L_SGPT_V<=M6_GVHD_A_L_SGPT_U_V
.<M6_GVHD_A_L_ALK_V<=M6_GVHD_A_L_ALK_U_V
M6_GVHD_LIV_ABN
```

Le score à V1 est calculé comme :

Score = 0 : Bilirubine normale WITH ALAT AND PAL < 3 ULN

```
(.<V1_GVHD_A_L_BILI_V<=V1_GVHD_A_L_BILI_U_V et
.<V1_GVHD_A_L_SGPT_V<3* V1_GVHD_A_L_SGPT_U_V  et
.<V1_GVHD_A_L_ALK_V<3* V1_GVHD_A_L_ALK_U_V )
```

Score = 1 : Bilirubine normale WITH 3 ULN<=ALAT < 5 UNL AND 3 ULN <=PAL<5 UNL
Score = 2 : Bilirubine élevée (>1*ULN) mais <= à 3 mg/dL OR ALAT >= 5 UNL OR PAL >=5 UNL (non mentionné dans article NIH).
Score = 3 : Bilirubine élevée > à 3 mg/dL

Lung : si FEV1 >=80% et FEV1<70 à V1. et dans le cas où la valeur de FEV1 est manquante, si le score est égal à 0

```
M6_GVHD_A_LU_FEV1_V>= 80
missing(M6_GVHD_A_LU_FEV1_V) and M6_GVHD_A_L=0
M6_GVHD_A_L
M6_GVHD_A_L_ABN
```

Calcul de réponse par organe :

Aucun calcul de réponse **par organe** (complète, partielle ou progression) n'est effectué si :

- « abnormalities present but explained entirely by non-GVHD documented cause » = Oui pour un organe à la visite considérée
- CR_*organe* , PR_*organe* et PD_*organe* sont alors mis à . (manquant)

Aucun calcul de réponse complète ou partielle **par organe** n'est effectué si :

- l'organe n'est pas atteint à V1 ou abnormalities present but explained entirely by non-GVHD documented cause » = Oui pour un organe à la visite V1.
- la progression est recherchée même si pas d'atteinte à V1
- CR_*organe* et PR_*organe* sont alors mis à . (manquant)

- **Partial response by organ**: en se basant sur les mêmes scores et en s'intéressant aux diminutions (ou augmentations) entre V1 (mêmes variables qu'indiquées précédemment mais qui commencent par « V1 » au lieu de « M6 ») et la visite considérée (M6,W6, W14, M9 ou M12)

- une diminution d'1 point pour les scores sur des échelles de 0 à 4 pour : Skin BSA, Skin features, Eyes, Joints, Gastro-oesophageal, Gastro-upper, Gastro-lower,

- une diminution de 2 points pour la somme des 3 sous-scores pour Mouth

- pour Lung, une augmentation entre V1 et la visite d'au moins 10% sur FEV1 avec FEV1 à V1 <70. Dans le cas de FEV1 manquants à V1 et ou M6, une diminution d'1 point sur le score 'lungs'

- pour Liver, (Bilirubine, ALAT ou PAL),

- si les valeurs à M6 sont en dessous des normales, la réponse est considérée Complète
- sinon la recherche d'une réponse partielle est effectuée : diminution de 50% de la valeur initiale
Le ratio est calculé ainsi : (M6-V1/V1)*100 et si le ratio est inférieur à -50 (mais pas de progression pour une des autres valeurs), il y a une réponse partielle

Global Partial response: au moins une réponse partielle sur un organe et avec une absence de progression pour un autre site

- Progressive disease by organ:

- peau, yeux, œsophage, tractus gastro-intestinal supérieur et inférieur : augmentation 1 point ou plus sur échelle de 0 à 3 = progression *SAUF* si changement de 0 à 1 (progression non spécifique)

- Joint: augmentation d'1 point ou plus = progression

- bouche : changement de 2 points ou plus sur la somme des 3 sous-scores

- pour Lung, diminution de 10 % avec FEV1 à V1 < 75% . Dans le cas de FEV1 manquants, augmentation d'1 point ou plus *SAUF* si changement de 0 à 1 (progression non spécifique)

- pour Liver, si l'une des valeurs à M6 est au-dessus de la normale pour Bilirubine, ALAT ou PAL, la recherche d'une progression est effectuée : la différence M6 – V1 est calculée et si la différence est supérieure à 2*ULN, il y a Progression.

Global progressive disease : si au moins un site avec une progression

Mixed response: si **Progressive disease** sur au moins un organe et **Partial response** sur au moins un autre

Extraits du protocole :

Table 4. Response determination for chronic GvHD (extrait du protocole)

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.

Appendix 2: Organ scoring of cGvHD

(NIH consensus criteria, Jagasia et al. Bone Marrow Transplant, 2015)

	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):*_____				

17.2 FACT-BMT

17.2.1 FACT-BMT items

FACT-BMT (4ème Version)

Veuillez indiquer votre réponse en entourant un seul chiffre par ligne et en tenant compte des 7 derniers jours.

	AUTRES SUJETS D'INQUIÉTUDE	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
BMT1	Je m'inquiète de ne pas pouvoir continuer à travailler (y compris le travail à la maison)	0	1	2	3	4
BMT2	Je me sens distant(e) des autres	0	1	2	3	4
BMT3	J'ai peur que la greffe ne réussisse pas	0	1	2	3	4
BMT4	Les effets du traitement sont pires que ce que j'imaginais	0	1	2	3	4
C6	J'ai bon appétit	0	1	2	3	4
C7	Je suis satisfait(e) de mon apparence physique	0	1	2	3	4
BMT5	Je peux me débrouiller seul(e)	0	1	2	3	4
BMT6	Je me fatigue facilement	0	1	2	3	4
BL4	Le sexe m'intéresse	0	1	2	3	4
BMT7	J'ai peur de ne plus pouvoir avoir d'enfants	0	1	2	3	4
BMT8	J'ai confiance en mes infirmières(iers)	0	1	2	3	4
BMT9	Je regrette d'avoir eu une greffe de la moelle osseuse	0	1	2	3	4
BMT 10	J'ai de la mémoire	0	1	2	3	4
Br1	Je suis capable de me concentrer	0	1	2	3	4
BMT 11	J'ai fréquemment des rhumes ou des infections	0	1	2	3	4
BMT 12	Je vois trouble	0	1	2	3	4
BMT 13	Je suis gêné(e) par un changement de goût des aliments	0	1	2	3	4
BMT 14	J'ai des tremblements	0	1	2	3	4
B1	J'ai le souffle court	0	1	2	3	4
BMT 15	Je suis gêné(e) par des problèmes de peau (éruptions démangeaisons)	0	1	2	3	4
BMT 16	J'ai du mal à aller à la selle	0	1	2	3	4
BMT 17	Ma maladie est une lourde épreuve pour ma famille proche	0	1	2	3	4
BMT 18	Le coût du traitement est un fardeau pour moi et pour ma famille	0	1	2	3	4

FACT-BMT (4ème Version)

Vous trouverez ci-dessous une liste de commentaires que d'autres personnes atteintes de la même maladie que vous ont jugés importants. **Veuillez indiquer votre réponse en entourant un seul chiffre par ligne et en tenant compte des 7 derniers jours.**

	BIEN-ÊTRE PHYSIQUE	**Pas du tout**	**Un peu**	**Moyen-nement**	**Beau-coup**	**Énormé-ment**
GP1	Je manque d'énergie	0	1	2	3	4
GP2	J'ai des nausées	0	1	2	3	4
GP3	À cause de mon état physique, j'ai du mal à répondre aux besoins de ma famille	0	1	2	3	4
GP4	J'ai des douleurs	0	1	2	3	4
GP5	Je suis incommodé(e) par les effets secondaires du traitement	0	1	2	3	4
GP6	Je me sens malade	0	1	2	3	4
GP7	Je suis obligé(e) de passer du temps allongé(e)	0	1	2	3	4

	BIEN-ÊTRE FAMILIAL/SOCIAL	**Pas du tout**	**Un peu**	**Moyen-nement**	**Beau-coup**	**Énormé-ment**
GS1	Je me sens proche de mes amis	0	1	2	3	4
GS2	Ma famille me soutient moralement	0	1	2	3	4
GS3	Mes amis me soutiennent	0	1	2	3	4
GS4	Ma famille a accepté ma maladie	0	1	2	3	4
GS5	Je suis satisfait(e) de la communication avec ma famille au sujet de ma maladie	0	1	2	3	4
GS6	Je me sens proche de mon (ma) partenaire (ou de la personne qui est mon principal soutien)	0	1	2	3	4
Q1	*Quel que soit votre degré d'activité sexuelle en ce moment, veuillez répondre à la question suivante. Si vous préférez ne pas y répondre, cochez cette case* ☐ *et passez à la section suivante.*					
GS7	Je suis satisfait(e) de ma vie sexuelle	0	1	2	3	4

FACT-BMT (4ème Version)

Veuillez indiquer votre réponse en entourant un seul chiffre par ligne et en tenant compte des 7 derniers jours.

	BIEN-ÊTRE ÉMOTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GE1	Je me sens triste	0	1	2	3	4
GE2	Je suis satisfait(e) de la façon dont je fais face à ma maladie	0	1	2	3	4
GE3	Je perds espoir dans le combat contre ma maladie	0	1	2	3	4
GE4	Je me sens nerveux (nerveuse)	0	1	2	3	4
GE5	Je suis préoccupé(e) par l'idée de mourir	0	1	2	3	4
GE6	Je suis préoccupé(e) à l'idée que mon état de santé puisse s'aggraver	0	1	2	3	4

	BIEN-ÊTRE FONCTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GF1	Je suis capable de travailler (y compris le travail à la maison)	0	1	2	3	4
GF2	Mon travail (y compris le travail à la maison) me donne de la satisfaction	0	1	2	3	4
GF3	Je suis capable de profiter de la vie	0	1	2	3	4
GF4	J'ai accepté ma maladie	0	1	2	3	4
GF5	Je dors bien	0	1	2	3	4
GF6	J'apprécie mes loisirs habituels	0	1	2	3	4
GF7	Je suis satisfait(e) de ma qualité de vie actuelle	0	1	2	3	4

French (Universal)

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17.2.2 Details of FACT-BMT calculation

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17.3 LEE SYMPTOM SCALE

The Lee Chronic GVHD Symptom Scale is a 30 item instrument with 7 subscales (skin, eyes, mouth, lung, nutrition, energy and psych) containing 2-7 items. Response options for "let us know if you have been bothered by any of the following in the past month" range from 0-4 (Not at all, Slightly, Moderately, Quite a bit, Extremely). Some investigators have used the scale in reference to the past 7 days. (Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; 8:444-452)

Subscale name	Number of items	Items
Skin	5	a. Abnormal skin color b. Rashes c. Thickened skin d. Sores on skin e. Itchy skin
Eye	3	f. Dry eyes g. Need to use eyedrops frequently h. Difficulty seeing clearly
Mouth	2	i. Need to avoid certain foods due to mouth pain j. Ulcers in mouth
Lung	5	l. Frequent cough m. Colored sputum o. Shortness of breath at rest p. Need to use oxygen **aa. Fevers**
Nutrition	5	**k. Receiving nutrition from an intravenous line or feeding tube**

		q. Difficulty swallowing solid foods r. Difficulty swallowing liquids s. Vomiting t. Weight loss
Energy	7	**n. Shortness of breath with exercise** **u. Joint and muscle aches** **v. Limited joint movement** **w. Muscle cramps** **x. Weak muscles** y. Loss of energy z. Need to sleep more/take naps
Psych	3	bb. Depression cc. Anxiety dd. Difficulty sleeping

Bold indicates items that are scored under a different subscale than where they are located

Scoring rules:

1. Note that the subscales do not conform exactly to the categories in the patient survey.
2. Subscales may be scored if 50% of more of the items in the subscale are completed.
3. Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a “0” and “100” means that all answered items were a “4”
4. Missing items are not included in the scoring.
5. The summary score is the average of the subscale scores, as long as 4 or more subscales are available.
6. Higher scores indicate more severe symptoms.
7. A clinically meaningful difference for each subscale or the summary score is considered to be half a standard deviation of the baseline score for the population, based on the distribution method of determining clinically meaningful changes.