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2. SYNOPSIS

Name of Sponsor/Company: MEDSENIC	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: TRISENOX®, ARSCIMED®		
Name of Active Ingredient: Arsenic trioxide		

Title of Study:
Phase II study of first line treatment of Chronic Graft versus Host Disease with Arsenic Trioxide (GvHD-ATO Study)

Study Centre(s)/Investigator(s):
Eleven (11) centers were planned to open. Eight (8) centers eventually opened and five (5) of them included patients. Pr Mohamad MOHTY was the coordinating Investigator. Full details of all Investigators are available in Section 16, Appendix 16.1.4.

Publication (Reference):
None as of 29/JUN/2021.

Study Period: First Subject First Visit: 30/NOV/2016 Last Subject Last Visit: 22/JUN/2020	**Phase of Development:** Phase II

Objectives:

Main Objective

- To improve the response rate (complete and partial remission) at 6 months after diagnosis of chronic graft versus host disease (GvHD) and treatment with arsenic trioxide (ATO) in combination with Prednisone with or without Ciclosporine as a first line treatment.

Secondary Objectives

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

Methodology:
Prospective, national, multicenter, non-randomized Phase II study**.**

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Number of Subjects (Planned, Consented, Randomized and Analyzed):

- Planned: 24
- Entered: 22
- Treated: 21
- Completed: 18
- Analyzed: 21
- Safety Population: 21
- Full Analysis Set Population: 20
- Per Protocol Population: 17

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

- Adult patients (≥18 years) who had received a first allogeneic stem cell transplantation for a hematological disease (any source of hematopoietic stem cells was authorized; any category of conditioning regimen prior to allo-SCT was authorized; any type of stem cell donors was authorized);
- Confirmed diagnosis of a first episode of chronic GvHD requiring systemic immunosuppressive therapy (any prior GvHD prophylaxis previously used was accepted). Chronic GvHD diagnosis was defined according to the NIH Working Group Consensus. Chronic GvHD diagnosis was based on the evaluation of the severity of the different clinical manifestations including:
  a/ Performance status evaluation;
  b/ Cutaneous evaluation measured by the percentage of extension or the presence of sclerotic features. If relevant, confirmation with a biopsy was to be performed whenever possible;
  c/ Oral symptoms;
  d/ Ocular symptoms;
  e/ Gastro-intestinal symptoms;
  f/ Evaluation of liver involvement (total bilirubin, transaminases and alkaline phosphatases);
  g/ Pulmonary function evaluation;
  h/ Evaluation of the musculoskeletal manifestations, especially the amplitude of the relevant articulations;
  i/ Genital tract symptoms.
- Signed informed consent;
- Absence of contra-indications to the use of arsenic trioxide (ATO);
- Subjects affiliated with an appropriate social security system;
- Men had to 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 were of childbearing potential had to have a negative serum pregnancy test and to agree to use a medically acceptable method of contraception throughout the study

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and for 3 months following the end of the study;
- Patient who were 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 who were developing acute GvHD (whether early or "late onset" form);
- Patients who were developing overlap GvHD as defined by the 2015 NIH Working Group Consensus (presence of one or more acute GvHD manifestations in a patient with a diagnosis of chronic GvHD);
- A "mild" form of chronic GvHD not requiring systemic immunosuppressive therapy;
- A "moderate" form of chronic GvHD limited to one organ site not requiring systemic immunosuppressive therapy;
- Patient who were 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 etc.);
- Significant arrhythmias, electrocardiogram (EKG) abnormalities:
- Congenital QT syndromes;
- History or presence of significant ventricular or atrial tachyarrhythmia;
- Clinically significant resting bradycardia (< 50 beats per minutes);
- QTc > 450 msec for men and > 470 msec for women on screening EKG (using the QTcF formula);
- Right bundle branch block plus left anterior hemiblock, bifascicular block.
- Central or peripheral neuropathy;
- Neutrophils $< 0.5 \times 10^9$/L ;
- Platelets $< 50 \times 10^9$/L ;
- Potassium ≤ 4 mEq/l* ;
- Magnesium ≤ 1.8 mg/dl* ;
- Calcium ≤ 2.15 mmol/l* ;
- Hepatic impairment due to a suspected or proven liver damage, other than direct hepatic cGvHD involvement ;
- PT < 50% ;
- Renal impairment (creatinine ≥ 100 µmol/l) ;
- Uncontrolled systemic infection which in the opinion of the investigator was associated with an increased risk of 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.

DocuSign Envelope ID: 655C6EEB-152B-43E7-A8F3-414D3C87D690

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

Reference therapies, dose and mode of administration:
NA

Investigational medicinal products, dose and form of administration:

- TRISENOX® (Arsenic trioxide) manufactured by TEVA (aqueous sterile, clear, colorless 1mg/mL - 10mL glass ampoule) administered by intravenous infusion (0.15mg/kg/infusion each day on days 1-5, 3 times per week during the second week, 2 times per week during the third week and one time during the fourth week.
- ARSCIMED® (Arsenic trioxide) manufactured by Institut de Recherche Pierre Fabre (IRPF) (aqueous sterile, clear, colorless 1mg/mL - 10mL vial) administered by intravenous infusion (0.15mg/kg/infusion each day on days 1-5, 3 times per week during the second week, 2 times per week during the third week and one time during the fourth week.

Duration of Treatment:
One cycle of four (4) weeks composed of 11 administrations.
Patients with a partial response after the first cycle of ATO were eligible to a second cycle administered with a delay of 8 weeks to a maximum of 11 weeks between two cycles.

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

Efficacy failure:
Treatment failure were defined by:

- Initiation of a new systemic treatment for chronic GvHD;
- Recurrent or progressive malignancy;
- Death

Early treatment failure was defined as treatment failure at week 6 post ATO.
Failure-free survival (FFS) was estimated at M6 and M12.

DocuSign Envelope ID: 655C6EEB-152B-43E7-A8F3-414D3C87D690

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

Statistical Methods:
The statistical analysis was performed using the 9.4 SAS software (SAS Institute, Cary, NC, USA).

Populations:

Safety Analysis (SA):	All patients included in the study for whom there is any evidence that they received at least one ATO infusion
Full Analysis Set (FAS):	All patients who entered the study, completed their first cycle of ATO and for whom the response at Week 6 after diagnosis of chronic GvHD has been evaluated.
Per Protocol (PP):	All patients who were in the FAS and did not have a major protocol deviation.

Qualitative data are described in frequency and percentage and are represented using histograms of distribution. Quantitative data are summarized by mean, standard deviation, median, and extreme values.

Primary efficacy analysis:
The proportion of response at 6 months (CR or PR) was estimated and presented with its 95% exact confidence interval (Clopper-Pearson). The null hypothesis H0: $P \leq P0$ was to be rejected in favor of the alternative hypothesis H1: $P > P1$ if the lower bound of the 95% CI was higher than 60%.

Secondary efficacy analysis:
- Failure
- Early efficacy failure (W6).
- Estimation of the failure-free survival at M6 and M12
- Death from any cause: estimation of the overall survival at M6 and M12
- Death or progression / relapse of the underlying hematological malignancy: estimation of the progression-free survival at M6 and M12
- Death from other cause than relapse of the underlying hematological malignancy: estimation of the non-relapse mortality at M6 and M12
- Death of infectious and non-infectious origin: estimation of the transplant-related mortality
- Definitive Prednisone dose reduction of at least 30% with death and early withdrawal

DocuSign Envelope ID: 655C6EEB-152B-43E7-A8F3-414D3C87D690

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considered as competing events;
- Definitive weaning from Prednisone with death and early withdrawal considered as competing events;

For survival rates estimations, the cumulative risk was estimated at W6, M6, and M12 based on the Kaplan-Meier model.

Descriptive statistics were provided for:
- Corticosteroids dosage at each month, percentage of reduction in corticosteroids dosage from baseline at each month;
- 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.
- Evolution from baseline of overall and by-organ cGvHD activity at each visit 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.

Safety analysis:
Tolerability and safety of ATO in combination with Prednisone, with or without Ciclosporine, in patients with chronic GvHD after allo-SCT.

Sample size:
Based on results from the literature, the hypothesis for the primary endpoint was an improvement in response rate (CR+PR) at 6 months after the diagnosis of chronic GvHD and start of corticosteroids, ATO, with or without Ciclosporine, between 60% and 85%.
Using a one-step A'Hern procedure (and anticipating a dropout rate around 10%), 24 (21+3) patients were needed (1). If the number of successful cases was 17 or more among the 21 patients, the hypothesis that the CR rate at 6 months was less than 60% could be rejected with a target error rate of 0.05 (alpha probability). The beta probability in this case was 0.2.

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Results

Patients disposition and baseline characteristics

Twenty-two (22) patients were included in the study. Of them, 21 (95.5%) were involved in the Safety set as one patient did not receive any ATO infusion (he experienced severe leukemia relapse prior to first infusion of treatment with ATO). Twenty patients (95.3%) were accounted in the FAS population whereas one patient was excluded from the FAS. This patient sustained a hepatic toxicity (SAE) after 2 infusions with ATO, decided not to resume the treatment after normalization of her liver values and did not undergo W6 visit. Seventeen (17; 81.0%) patients were accounted in the PP population (exclusion of 3 patients with protocol deviations: 2 patients with late M6 visit (+ 21 and 26 days from the theoretical date respectively) and 1 patient with a half-dose in part of the 1st cycle of treatment with ATO).

Among the 21 patients having received at least 1 infusion of ATO, 52.4% were men and mean age at inclusion was 59.6 ± 9.6 years old. Per clinician assessment, mean cGvHD severity score on a 0-10 scale was 5.7 ± 1.7 (Median: 6.0) at baseline. Fourteen (14; 66.7%) patients were considered having severe cGvHD, 6 (28.6%) had moderate cGvHD and 1 (4.8%) had a mild cGvHD. Six patients were receiving Ciclosporine at entry in the study.

Twelve (12; 57.1%) patients had one cycle of treatment with ATO and 9 (42.9%) had two cycles of treatment with ATO. Ten patients had a concomitant treatment with Ciclosporine at one point during the study: 6 continued the treatment ongoing at entry and 4 patients initiated a treatment with Ciclosporine during the study. At entry, all patients received corticosteroids at a mean dose of 0.93 ± 0.21 mg/kg/day.

Primary efficacy analysis:

In the FAS population, 75.0% [50.9%; 91.3%] of patients achieved complete (CR) or partial (PR) clinical response at 6 months per investigator evaluation (main endpoint); 35.0% achieved CR and 40.0% PR. In the PP population, 82.4% [56.2%; 96.2%] of patients achieved CR or PR with 41.2% CR and 41.2% PR. Similar results were obtained in the FAS population when computing the response according the NIH consensus criteria: 75.0% [50.9%; 91.3%] achieved CR or PR at M6 (CR 20.0%, PR 55.0%). The null hypothesis response rate ≤ 60% could not be rejected (partly for a lack of power) but the crude clinical response rate was in line with the study expectations.

Secondary efficacy analysis:

- Early failures

No patient experienced early failure.

- Failure-free survival

In the FAS population, the estimated failure-free survival rate was 90.0% [65.6%;97.4%] at M6 and 65.0% [40.3%;81.5%] at M12. Two patients received additional systemic treatment for cGvHD before M6. Between M6 and M12, 4 patients received additional systemic treatment for cGvHD and one patient died.

- Disease progression-free survival

In the FAS population, the estimated progression-free survival was 95.0% [69.5%;99.3%] at M6 and 83.8% [57.7%;94.5%] at M12. cGvHD progression was diagnosed in one (5.0%) patient within 6 months after first ATO infusion and in 2 (15.0%) patients between M6 and M12.

- Overall survival

One patient died after 6.4 months from a septic shock. The estimated overall survival rate was 100% at M6 and 95.0% [69.5%;99.3%] at M12. Of note, 1 more patient died after the theoretical M12 date but before the effective M12 visit.

- Non-relapse mortality

The estimated non-relapse mortality rate was 5.0% [0.3%;21.1%] at M12.

PP population results supported the results obtained in the FAS population.

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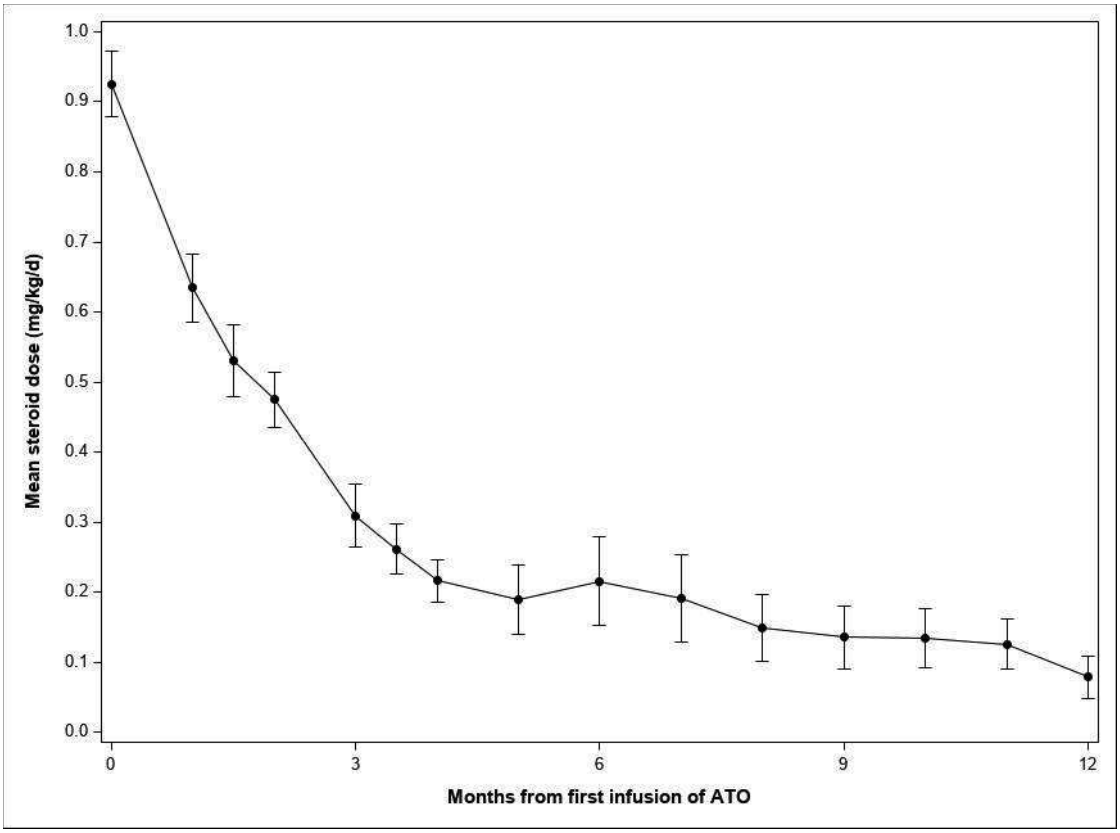
- Sparing corticosteroids

Mean daily dose of Prednisone was 0.92 ± 0.21 mg/Kg (median: 0.97 mg/Kg/d) at baseline, decreased quickly after first ATO infusion, and reached 0.22 ± 0.29 mg/Kg/d (median: 0.13mg/Kg/d) at M6 and 0.08 ± 0.13 mg/Kg/d (median: 0.0 mg/Kg/d) at M12. Percent change from baseline was -74.6 ± 32.7% (median: -86.2%) at M6 and -91.0 ± 14.6% (median: -100.0%) at M12. Six/20 patients (30.0%) at M6 and 9/19 patients (47.4%) at M12 were definitively weaned from Prednisone.



Mean dose of Prednisone equivalent in milligrams per kilograms per day with standard error of the mean - FAS Population

- Quality of life
  - Lee symptoms scale

In the FAS population, global LSS score was 29.5 ± 18.6 (median: 27.7; min: 7.1; max: 73.2) at baseline, decreased to 21.8 ± 15.3 / 100 (median: 19.7; min: 1.3; max: 55.4) at M6 and to 21.4 ± 13.9 / 100 (median: 22.7; min: 1.8; max: 43.3) at M12. There was a significant decrease from baseline: -8.5 ± 20.14 (median: -10.2) points at M6 (p=0.030) which was not significant anymore at M12: -5.2 ± 20.6 (median -1.0; p=0.189) with high between-individual heterogeneity.

  - FACT-BMT

FACT-BMT was only partially responded in most of patients, limiting the interpretation of the results.

  - Chronic Form B

At baseline, self-evaluation of severity was assessed by 13 patients. Three (23.1%) estimated their cGvHD as severe, 8 (61.5%) as moderate and 2 (15.4%) as mild. Between baseline and M6, 4/10 (40.0%) patients estimated that their cGvHD improved, 4/10 (40.0%) considered that there was neither improvement nor worsening and 2/10 (20.0%) considered that their condition worsened. Between baseline and M12, 1/8 (12.5%) patient considered that the disease worsened, 5/8 (62.5%) that it did not vary and 2/8 (25.0%) that it improved.

DocuSign Envelope ID: 655C6EEB-152B-43E7-A8F3-414D3C87D690

- Investigator's evaluation of GvHD activity

According to the investigator's assessment, in the FAS population, 13 (65.0%) patients had severe cGvHD, 6 (30.0%) had moderate and 1 (5.0%) had mild cGvHD at baseline. Of patients with severe cGvHD at baseline, 2 (15.4%) remained severe at M6, 3 (23.1%) had moderate cGvHD at M6, 3 (23.1%) had mild cGvHD, and 5 (38.5%) had no sign of cGvHD. Of patients with moderate cGvHD at baseline, 2 (33.3%) worsened and had severe symptoms at M6. Three (3; 50.0%) did not improve nor worsened at M6 and 1 (16.7%) had no more cGvHD symptoms at M6. Finally, the patient with mild cGvHD at baseline improved and had no symptom at M6.
At M12, of 13 patients with severe cGvHD at baseline, 2 died before M12. Of the 11 survivors, 2 (18.2%) still had severe cGvHD, 1 (9.1%) had moderate cGvHD, 4 (34.4%) had mild cGvHD and 4 (36.4%) had no sign of cGvHD. Of the 6 patients with moderate cGvHD at baseline, 1 (16.7%) worsened and showed severe symptoms at M12, 1 (16.7%) still had moderate symptoms, 2 (33.3%) improved and had mild symptoms. Two (2; 33.3%) had no sign of cGvHD. Finally, the patient who showed mild cGvHD at baseline had moderate symptoms at M12.

Safety analysis:
197 AEs were reported in 21 (100%) patients, among which 22 in 9 (43.0%) patients were serious (SAEs). Fourteen (14) AEs in 7 (33.0%) patients could not be excluded from being related to treatment. Among them, 2 were serious (2 hepatotoxicities) of which 1 (4.8%) led to patient withdrawal. Finally, 2 SAEs (one septic shock and one encephalopathy, both not related to the study treatment) led to the death of 2 (9.5%) patients.

Summary - Conclusions:
In this non comparative study, the observed rate of response (PR+CR) in the FAS population was 75.0% [50.9%; 91.3%] at 6 months (main endpoint). The lower bound of the 95% CI was to be compared with a theoretical minimal rate of 60% for significance, then the null hypothesis cannot be formally rejected. However, the clinical hypothesis was based on a 60%-85% crude response rate and the results were in line with the study expectations. These numbers must be compared with the overall response rate observed with corticosteroids alone or in combination with Ciclosporine which barely reaches 50% with high dose Prednisone equivalent (2 mg/kg/d). They must also be compared with results obtained with new agents. A recent meta-analysis, which included 8 different studies (7 agents) that focused on cGvHD, reported response rates between 34% and 80%, including products showing safety issues or immediate disease progression after cessation of the treatment cycle. Our overall response rate is in line with results obtained with new agents and far larger than the response rate observed with CS alone or in combination with calcineurin inhibitors.
Furthermore, mean daily dose of Prednisone decreased quickly after first ATO infusion with a percent change from baseline of 74.6 ± 32.7% at M6 and 91.0 ± 14.6% at M12. ATO allowed a quick and marked decrease in Prednisone (0.13mg/Kg/d at M6 and 0.08 ± 0.13 mg/Kg/d at M12). Median time to definitive decrease of Prednisone dose by at least 30% was 1.08 months (33 days). Six/20 patients (30.0%) were weaned from Prednisone at M6 and 9/19 patients (47.4%) at M12. The potential of ATO to reduce exposure to CS compared favorably with those of new agents. Indeed, efforts should be made to use the minimum dose that is sufficient to control cGvHD manifestations
Finally, low B-cell counts and increased risk of infections have long been recognized in patients with cGvHD. The risk is majored by the use of systemic CS and Ciclosporine. In our study, one patient died from a septic shock which was not related to ATO.