Clinical trial results:
Phase II study of first line treatment of Chronic Graft versus Host Disease with Arsenic Trioxide

Summary

EudraCT number	2016-002358-18
Trial protocol	FR
Global end of trial date	22 June 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	GvHD-ATO Study Synopsis (extract from the CSR Version 1.0 – 29JUN21) (CSR_GvHD-ATO_FULL_V1_FINALE_29JUN2021_Synopsis extract.pdf)

Trial information

Trial identification

Sponsor protocol code	GMED16-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02966301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MEDSENIC
Sponsor organisation address	204 avenue de Colmar, Strasbourg, France, 67100
Public contact	François RIEGER, MEDSENIC, 33 671733159, fr@medsenic.org
Scientific contact	François RIEGER, MEDSENIC, 33 671733159, fr@medsenic.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2020
Global end of trial reached?	Yes
Global end of trial date	22 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 first line treatment

Protection of trial subjects:

Each patient has been followed during the whole study with regular visits of follow up and SAE have been declared to the pharmacovigilance entity.
Assessment of quality of live at each evaluation visit (Inclusion, W6, W14, M6, M9 and M12).
In addition, a meeting of the IDMC of the study has been organized every year during the study (4 meetings) in order to review the safety data. Conclusions of these meetings have been included into the DSUR adressed to the national competent authorities.

Background therapy:

No background therapy.

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	15
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period from the 30/NOV/2016 (Toulouse-site 05) to the 03/JUN/2019 (Caen-site 06) in FRANCE.
Last subject Last Visit : 22/JUN/2020.

Pre-assignment

Screening details:

Site 1 : 6 screened / 6 Included / 5 treated
Site 2: 2 screened / 2 Included / 2 treated
Site 3: 1 screened / 1 Included / 1 treated
Site 5: 6 screened / 4 Included / 4 treated
Site 6: 9 screened / 9 Included / 9 treated
Site 8: 2 screened / 0 Included
Site 9: 1 screened / 0 Included
Site 10: 2 screened / 0 Included

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Arsenic Trioxide

Arm description:

One group of treatment : 0.15mg/kg/d of arsenic trioxide

Arm type	Experimental
Investigational medicinal product name	Arsenic Trioxide
Investigational medicinal product code	
Other name	Trisenox,Arscimed
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

As soon as the diagnosis of chronic GvHD requiring systemic immunosuppressive therapy was confirmed, patients were included. They received corticosteroids at 1 mg/kg/day and Ciclosporine A (if relevant).

Number of subjects in period 1[1]	Arsenic Trioxide
Started	21
Completed	21

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: On the 22 enrolled patients, 1 patient has not been treated due to rellapse of the leukemia immediately after enrollement. As a consequence, the "started" number of patients used in the baseline is 21, which is consistent with the Safety population.

Period 2

Period 2 title	M6 period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Arsenic Trioxide

Arm description:

One group of treatment : 0.15mg/kg/d of arsenic trioxide

Arm type	Experimental
Investigational medicinal product name	Arsenic Trioxide
Investigational medicinal product code	
Other name	Trisenox,Arscimed
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

As soon as the diagnosis of chronic GvHD requiring systemic immunosuppressive therapy was confirmed, patients received in addition to Ciclosporine A (if relevant) and corticosteroids 1 mg/kg/day, ATO 0.15 mg/kg/day over a 4 weeks period (one cycle).
The treatment plan was indicative for one cycle (=11 infusions) within 10 days of starting Prednisone 1mg/kg/day.
Patients in partial response after the 1st cycle of ATO were eligible to receive a second cycle of ATO as consolidation therapy. A delay of 8 weeks to a maximum of 11 weeks was to be observed between the two cycles of ATO therapy.

Number of subjects in period 2	Arsenic Trioxide
Started	21
Completed	20
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	21	21	
Age categorical			
Subjects are Adult patients (≥18 years)			
Units: Subjects			
Adults (≥18 years)	21	21	
Gender categorical			
Male and female subjects			
Units: Subjects			
Male & Female	21	21	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

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.

Subject analysis set title	Safety Analysis (SA)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients included in the study for whom there is any evidence that they received at least one ATO infusion

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who were in the FAS and did not have a major protocol deviation.

Reporting group values	Full Analysis Set (FAS)	Safety Analysis (SA)	Per Protocol (PP)
Number of subjects	20	21	17
Age categorical			
Subjects are Adult patients (≥18 years)			
Units: Subjects			
Adults (≥18 years)	20	21	17
Gender categorical			
Male and female subjects			
Units: Subjects			
Male & Female	20	21	17

End points

End points reporting groups

Reporting group title	Arsenic Trioxide
Reporting group description:	
One group of treatment : 0.15mg/kg/d of arsenic trioxide	
Reporting group title	Arsenic Trioxide
Reporting group description:	
One group of treatment : 0.15mg/kg/d of arsenic trioxide	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
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.	
Subject analysis set title	Safety Analysis (SA)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients included in the study for whom there is any evidence that they received at least one ATO infusion	
Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who were in the FAS and did not have a major protocol deviation.	

Primary: Efficacy success

End point title	Efficacy success[1]
End point description:	
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.	
End point type	Primary
End point timeframe:	
Month 6 after the first ATO infusion	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: One arm study, only percentage, no comparison.

End point values	Arsenic Trioxide	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	17	
Units: Number of subjects				
Complete Remission (CR) and Partial Remission (PR)	15	15	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Failure free survival

End point title	Failure free survival

End point description:

Treatment failure were defined by:
- Initiation of a new systemic treatment for chronic GvHD;
- Recurrent or progressive malignancy;
- Death

End point type	Secondary

End point timeframe:

Failure-free survival (FFS) was estimated at M6 and M12

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
M6	90 (65.6 to 97.4)			
M12	65 (40.3 to 81.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-relapse mortality (NRM)

End point title	Non-relapse mortality (NRM)

End point description:

Non-relapse mortality (NRM) of infectious and non-infectious origin

End point type	Secondary

End point timeframe:

M6 and M12

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
M6	100 (100 to 100)			
M12	5 (0.3 to 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: overall survival (OS)	
End point type	Secondary
End point timeframe: M6 and M12	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
M6	100 (100 to 100)			
M12	95 (69.5 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sparing of corticotherapy

End point title	Sparing of corticotherapy
End point description: patients from long-term use of corticosteroids (and their long-term side effects)	
End point type	Secondary
End point timeframe: Dose from baseline, M6, and M12 (mg/kg per day)	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: dosage form				
arithmetic mean (standard error)				
Baseline	0.92 (± 0.21)			
M6	0.22 (± 0.29)			
M12	0.08 (± 0.13)			

Attachments (see zip file)	Sparing corticosteroids/Sparing corticosteroids graph.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability and safety

End point title	Tolerability and safety

End point description:

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

End point type	Secondary

End point timeframe:

During the whole study

End point values	Arsenic Trioxide	Safety Analysis (SA)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: AE & SAE number				
AE	197	197		
SAE	22	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the whole study.

Adverse event reporting additional description:

197 AEs were reported in 21 patients, among which 22 in 9 patients were serious (SAEs). 14 AEs in 7 patients could not be excluded from being related to treatment. Among them, 2 were serious (2 hepatotoxicities) of which 1 led to patient withdrawal. 2 SAEs (one septic shock and one encephalopathy) both not related to the study product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 21 (42.86%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Nervous system disorders			
Encephalopathy	Additional description: Fatal encephalopathy started on Nov 15th, 2018 and led to patient's death on Dec 28th, 2018, before this patient could perform M12 visit. Investigator considered that there was not related to the IMP.		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epilepsy			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Oedema peripheral				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatitis acute				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Lung disorder				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock	Additional description: The patient was hospitalized several times in 2017 for pneumopathy and pneumonia. On October the patient was hospitalized for septic shock. Investigator considered that the SAE is not related to the study product.		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Genital herpes			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia pyelonephritis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)		
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Venous thrombosis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cyst	Additional description: Related AE		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Medical device pain			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Oedema peripheral	Additional description: 1 related AE		
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	8		
Pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	7		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Hypogammaglobulinaemia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Vulvovaginal erythema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 21 (42.86%)		
occurrences (all)	10		
Dyspnoea			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Epistaxis			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Lung disorder			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Obstructive airways disorder			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pulmonary mass			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Rales			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Respiratory distress			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Investigations			
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
CD4 lymphocytes decreased			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Electrocardiogram QT prolonged	Additional description: Related AE		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Atrial fibrillation			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Peroneal nerve palsy			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: 1 related AE		
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Thrombocytopenia	Additional description: 1 related AE		
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Ocular discomfort			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Visual acuity reduced			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal pain	Additional description: One AE related		
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Diarrhoea	Additional description: 2 related AE		
subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	10		
Dysphagia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nausea	Additional description: One AE related		
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Odynophagia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Vomiting	Additional description: Related AE		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			

Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Ingrowing nail			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Lichenification			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Nail bed bleeding			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Myalgia	Additional description: Related AE		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Infections and infestations			

Bronchitis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Campylobacter infection				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences (all)	2			
Cytomegalovirus infection				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences (all)	3			
Device related infection				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences (all)	2			
Epstein-Barr virus infection				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Escherichia urinary tract infection				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences (all)	2			
Fungal infection				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Genital herpes				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Genital infection fungal				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Klebsiella infection				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences (all)	1			

Pneumonia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Pseudomonal bacteraemia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Respiratory syncytial virus infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Rhinovirus infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Staphylococcal sepsis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 7		
Viral infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Fluid retention subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Hyperkalaemia			

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Hypokalaemia	Additional description: 1 related AE		
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Malnutrition			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2017	Protocol V4.0 Updating of the list of investigators. Modification of exclusion criteria for fitting with the clinical condition of patients with cGvHD. Precisions regarding the modalities of administration of ATO and associated treatments. Modifications of the study planning. Precisions regarding the conditioning of ATO. Precisions regarding the safety management. Extension of the inclusion period.
06 October 2017	Protocol V5.0 Replacement of the study treatment TRISENOX® (TEVA) by ARSCIMED® (Pierre Fabre) for newly included subjects.
06 March 2018	Protocol V.6.0 Extension of the inclusion period. Suppression of one exclusion criteria "GvHD occurring following donor lymphocytes infusion (DLI)", in order to adapt the protocol at the current hospital practice, as the DLI is more and more used as a preventive treatment for recurrence of initial leukemia. Updating of the Sponsor's mailing address. Updating of the list of investigators.
18 December 2018	Protocol V7.0 Extension of the inclusion period. Updating of the list of investigators. Modification of the section dealing data protection with GDPR law compliance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: