Clinical trial results:
Clinical phase II trial to evaluate the safety and efficacy of treosulfan combined with cytarabine and fludarabine prior to autologous haematopoietic stem cell transplantation in elderly patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome.

Summary

EudraCT number	2008-000664-16
Trial protocol	IT
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	FLATauto

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03961919
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	San Raffaele Hospital IRCCS
Sponsor organisation address	VIA OLGETTINA 60 Milano Italia, Milan, Italy, 20132
Public contact	ciceri.clinicaltrials@hsr.it, San Raffaele Hospital IRCCS Hematology and BMT Unit, +39 0226439396, ciceri.clinicaltrials@hsr.it
Scientific contact	ciceri.clinicaltrials@hsr.it, San Raffaele Hospital IRCCS Hematology and BMT Unit, +39 0226439396, ciceri.clinicaltrials@hsr.it

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	19 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of disease free survival from first Complete Remission (CR)
Evaluation of disease-free survival (DFS) duration from documented first CR of AML or MDS with intermediate 2 or high IPSS (International Prognostic Score System).
[Time Frame: 2 years after transplantation]

Protection of trial subjects:

Common protection due to Clinical Trial partecipant:
- Pharmacovigilance
- Ethical Supervision
- Clincial peer reviewing

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	0
From 65 to 84 years	15

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Versione:Livello:HLT
Codice: Termine:LEUCEMIE ACUTE MIELOIDI

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	15
Number of subjects completed	15

Period 1

Period 1 title	Inclusion (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment

Arm description:

Single Group Assignment
Number of Arms: 1
Masking: None (Open Label)

Arm type	Experimental
Investigational medicinal product name	FLUDARA
Investigational medicinal product code	1
Other name	Fludarabina
Pharmaceutical forms	Powder and solvent for dispersion for injection
Routes of administration	Solution for injection

Dosage and administration details:

Concentrazione (numero): 50
Unità di concentrazione: mg milligram(s)
Note: 50 mg/fiala

Investigational medicinal product name	ARACYTIN
Investigational medicinal product code	2
Other name	ARA-C
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

Concentrazione (numero): 50
Unità di concentrazione: mg/l milligram(s)/litre

Investigational medicinal product name	TREOSULFANO
Investigational medicinal product code	2
Other name	TREOSULFANO
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Concentrazione (numero): 14
Unità di concentrazione: % percent

Investigational medicinal product name	GRANULOKINE 30
Investigational medicinal product code	4
Other name	Filgrastim
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Concentrazione (numero): 30
Unità di concentrazione: Munit million units
Note: 30 MU/ML

Number of subjects in period 1	Treatment
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Single Group Assignment Number of Arms: 1 Masking: None (Open Label)	

Reporting group values	Treatment	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	15	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	6	6	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Single Group Assignment
Number of Arms: 1
Masking: None (Open Label)

Subject analysis set title	Treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This is a single-arm, descriptive study. All efficacy and safety analyses will be performed on the Treosulfan-treated patients. Kaplan–Meier estimates will be used to describe disease-free survival (DFS) and overall survival (OS) with 95% confidence intervals. No formal statistical comparison with a control group will be performed.

Primary: Evaluation of disease free survival

End point title	Evaluation of disease free survival

End point description:

End point type	Primary

End point timeframe:

2 years after transplantation

End point values	Treatment
Subject group type	Reporting group
Number of subjects analysed	15
Units: days	
number (not applicable)	454

Statistical analyses

Statistical analysis title	Descriptive statistics

Statistical analysis description:

DFS will be analyzed using the Kaplan–Meier method. Median DFS and DFS rates at 1, 2 and 3 years post-autoHSCT will be reported with 95% confidence intervals. Patients who have not experienced disease relapse or death will be censored at last follow-up.

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	
Method	Kaplan–Meier method
Parameter estimate	Median

Notes:

[1] - This is a single-arm, non-comparative study.
Disease-free survival will be analysed descriptively using the Kaplan–Meier method. Median DFS and DFS rates at fixed time points with 95% confidence intervals will be reported. No formal statistical comparison between groups is planned.

[2] - This is a single-arm, descriptive study. No formal statistical comparison is performed; p-values are not applicable

Adverse events

Adverse events information	
Timeframe for reporting adverse events: day +90 after autotransplantation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11

Reporting groups	
Reporting group title	Adverse event

Reporting group description:

In the population of patients aged >65 years who received at least one dose of treosulfan and underwent autologous HSCT, adverse events were collected systematically from first dose until day +90 post-transplant. All events were coded using graded according to NCI-CTC v3.0. Non-serious adverse events occurring in ≥5% of patients were reported. Extra-hematologic toxicities had a median grade of 2 (range 0–4). One patient experienced grade 4 pancytopenia resulting in death due to invasive fungal infection.

Serious adverse events	Adverse event		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	10		
Nervous system disorders			
Polyradiculoneuropathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Death			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 10		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adverse event		
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 15 (53.33%)		
Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 1		
Nervous system disorders Neurologic Disorder subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 1		
Blood and lymphatic system disorders Extra-Hematologic toxicities subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 1		
Immune system disorders Gram negative-positive-molds subjects affected / exposed occurrences (all)	7 / 15 (46.67%) 1		
Hepatobiliary disorders Hepatic disorder subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 1		
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	7 / 15 (46.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2018	With this non-substantial amendment, the need to extend the patient recruitment period for the protocol in question until December 2013 is being notified. This need arises from the failure to reach the planned patient sample, currently 6 out of 15, within the scheduled timeframe. The delay is mainly due both to the presence of competing allogeneic transplant protocols for the 65-70 years age group and to the frequent, sometimes fatal morbidities in patients over 70 years old during the disease treatment phases preceding this study

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.

Patient recruitment was slowed down both by the presence of competing allogeneic transplant protocols at the center for the 65-70 years age group and by the frequent, sometimes fatal morbidities in patients over 70 years old during the disease treatm

Notes: