Clinical trial results:
Clinical phase II trial to evaluate the safety and efficacy of clofarabine and treosulfan conditioning prior to peripheral blood stem cells transplantation in paediatric and adult patients with advanced haematological malignancies

Summary

EudraCT number	2008-006972-31
Trial protocol	IT
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2021
First version publication date	07 May 2021

Trial information

Trial identification

Sponsor protocol code	Clo3o

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IRCCS Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20132
Public contact	Dept. of Haematology/Transplant Unit, IRCCS Ospedale San Raffaele, 0039 0226434289, ciceri.clinicaltrials@hsr.it
Scientific contact	Dept. of Haematology/Transplant Unit, IRCCS Ospedale San Raffaele, 0039 0226434289, 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 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety: Evaluation of cumulative incidence non-relapse mortality (NRM); Evaluation of cumulative incidence and severity of acute and chronic graft
vs. host disease (GvHD).
Efficacy: Engraftment; Evaluation of progression free survival (PFS); Evaluation of overall survival (OS); Evaluation of relapse incidence (RI).

Protection of trial subjects:

N.A.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 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: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	2
Adults (18-64 years)	40
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From November 2009 to November 2013, we enrolled 44 patients (median age 47 yers old), 36 affected by acute myeloid leukemia, 5 by acute lymphoblastic leukemia and 3 by myelodisplastic syndrome. The study was conducted in 4 Italian Bone Marrow Transplant Centers.

Pre-assignment

Screening details:

Both pediatric and adult patients were included (age range, 13-69 years), each with an available HLA-matched related or unrelated donor. HLA compatibility among donor-recipient pairs was assessed by 10-loci molecular typing (HLAA,-B, -C, -DRB1, -DQB1), with no more than a 2-allele disparity allowed.

Period 1

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

Arms

Arm title	Clo-Treo HSCT

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/mq within 60-120minutes i.v. (from day -6 to day -2)

Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

14 g/mq within 120 minutes i.v. (from day -6 to day -4)

Number of subjects in period 1	Clo-Treo HSCT
Started	44
Completed	44

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
Age continuous Units: years			
median	47		
full range (min-max)	13 to 69	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	22	22	
Disease diagnosis Units: Subjects			
AML	36	36	
MDS	3	3	
ALL	5	5	
Status at transplant Units: Subjects			
First CR	16	16	
Other CR	9	9	
Active disease	16	16	
Upfront	3	3	
Comorbidities (HCT-CI) Units: Subjects			
Zero	15	15	
1-2	12	12	
3-4	17	17	
Disease Risk Index (DRI) Units: Subjects			
Low	1	1	
Intermediate	26	26	
High	13	13	
Very High	4	4	
CMV serostatus (host/donor) Units: Subjects			
negative/negative	2	2	
negative/positive	2	2	
positive/negative	11	11	
positive/positive	29	29	
Donor-recipient HLA matching			

Units: Subjects			
MRD (10/10)	22	22	
MUD (8/10)	1	1	
MUD (9/10)	7	7	
MUD (10/10)	14	14	

Subject analysis sets	
Subject analysis set title	MRD Transplant
Subject analysis set type	Sub-group analysis
Subject analysis set description: Allogenic haematopietic stem cells were derived from a sibling	
Subject analysis set title	MUD Transplant
Subject analysis set type	Sub-group analysis
Subject analysis set description: Allogeneic haematopoietic stem cells were derived from a well-matched unrelated donor	

Reporting group values	MRD Transplant	MUD Transplant	
Number of subjects	22	22	
Age categorical Units: Subjects			
Age continuous Units: years			
median	43	50	
full range (min-max)	13 to 61	16 to 69	
Gender categorical Units: Subjects			
Female	13	9	
Male	9	13	
Disease diagnosis Units: Subjects			
AML	17	19	
MDS	3	0	
ALL	2	3	
Status at transplant Units: Subjects			
First CR	8	8	
Other CR	4	5	
Active disease	7	9	
Upfront	3	0	
Comorbidities (HCT-CI) Units: Subjects			
Zero	10	5	
1-2	5	7	
3-4	7	10	
Disease Risk Index (DRI) Units: Subjects			
Low	1	0	
Intermediate	14	12	
High	5	8	

Very High	2	2	
CMV serostatus (host/donor) Units: Subjects			
negative/negative	0	2	
negative/positive	1	1	
positive/negative	3	8	
positive/positive	18	11	
Donor-recipient HLA matching Units: Subjects			
MRD (10/10)	22	0	
MUD (8/10)	0	1	
MUD (9/10)	0	7	
MUD (10/10)	0	14	

End points

End points reporting groups

Reporting group title	Clo-Treo HSCT
Reporting group description: -	
Subject analysis set title	MRD Transplant
Subject analysis set type	Sub-group analysis
Subject analysis set description: Allogenic haematopietic stem cells were derived from a sibling	
Subject analysis set title	MUD Transplant
Subject analysis set type	Sub-group analysis
Subject analysis set description: Allogeneic haematopoietic stem cells were derived from a well-matched unrelated donor	

Primary: Cumulatve Incidence of Non Relapse Mortality (NRM)

End point title	Cumulatve Incidence of Non Relapse Mortality (NRM)[1]
End point description: NRM was defined as death without evidence of disease progression or relapse. Disease progressione or relapse was treated as competing event in the NRM analyses	
End point type	Primary
End point timeframe: Evaluation of the cumulative incidence of NRM on day +100	

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: This study is a non-controlled phase II study.
For efficacy comparison, mainly EBMT registry data or published papers will be used.
According to Simon's two-stage design method the total number of patients needed to asses an expected NRM of 20% was 45. The cumulative incidence method with competing risk was used for NRM.

End point values	Clo-Treo HSCT			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percent				
median (confidence interval 95%)	18 (7 to 30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence and severity of acute and chronic graft vs. host disease (GvHD)

End point title	Cumulative incidence and severity of acute and chronic graft vs. host disease (GvHD)
End point description:	
End point type	Secondary
End point timeframe: Evaluation of cumulative incidence and severity of aGvHD until day 100 and cGvHD during total follow-	

up.

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Engrafment

End point title	Primary Engrafment

End point description:

End point type	Secondary

End point timeframe:

Neutrophil engraftment was defined as a neutrophil count >= 5 x 109/L for more than 3 consecutive days; platelet engraftment was defined as a platelet count >= 20 x 109/L for more than 3 consecutive days in the absence of transfusions.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

1 year

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

1 year

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse incidence

End point title	Relapse incidence

End point description:

End point type	Secondary

End point timeframe:

1 year

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Between day -6 and day +28 the patient will be asked and examined by the investigator for the occurrence of AEs. This time period is assumed to be appropriate for the evaluation of adverse events directly related to the conditioning regimen.

Adverse event reporting additional description:

- patients’ charts
- laboratory reports
- doctor’s letters
- nurses documentation

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events were not collected.
Please see the publication for futher information.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	Review of the study design with definition of endpoints.
14 November 2011	Inclusion criteria modification: extension to patients with high-risk hematological malignancies; possibility of using for transplantation stem cells from bone marrow and not only PBSC (as standard for pediatric patients)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31605823