Clinical trial results:
Treosulfan and 4 Gy TBI based conditioning with Rapamycin-based GvHD prophylaxis for allogeneic stem cell transplantation in patients with haematological malignancies

Summary

EudraCT number	2011-001534-42
Trial protocol	IT
Global end of trial date	16 June 2016

Results information

Result version number	v1 (current)
This version publication date	08 July 2021
First version publication date	08 July 2021

Trial information

Trial identification

Sponsor protocol code	TrRaMM4Gy

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	16 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficay: Evaluation of progression free survival (PFS) at 365 days; Evaluation of engraftment; Evaluation of Overall survival (OS) and relapse incidence (RI)
Safety: Evaluation of of non-relapse mortality (NRM); Evaluation of cumulative incidence and severity of acute and chronic graft vs. host disease (GvHD).

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	64
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult patients with hematologic malignancies (leukemia, myeloma, lymphoma), candidates for allogeneic transplantation from related or unrelated mismatched donor

Period 1

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

Arms

Arm title	TrRaMM4Gy

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Treosulfan
Investigational medicinal product code	
Other name	Dihydroxybusulfan
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The investigational drug treosulfan is available as dry substance in vials of 1 g and 5 g and must be dissolved in 20 ml or 100 ml of water for injection respectively. A dosage of 14 g/m² will be administered intravenously within 120 minutes on 3 consecutive days (day -6, -5, -4).
Alkalisation of the urine by infusion of sodium bicarbonate solution is not recommended because of the pH-dependent activation of treosulfan

Investigational medicinal product name	Rapamycin
Investigational medicinal product code	
Other name	Rapamune, Sirolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational drug rapamycin is available as 1 mg tablet. It will be administred as a starting dose of 4 mg die from the day before the start of the conditioning (day -7), with a target serum concentration of 8-15 ng/ml by HPLC. Levels will be monitored three times weekly during hospitalization and then as clinically indicated.
Rapamycin will be continued till day +60 unless contraindicated because of toxicity or in case of disease progression or relapse. The drug will be tapered beginning at day +60 and eliminated by day +100, unless aGvHD occurred.

Number of subjects in period 1	TrRaMM4Gy
Started	67
Completed	64
Not completed	3
Physician decision	2
Screening failure	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	67	67	
Age categorical Units: Subjects			
Adults (18-64 years)	64	64	
From 65-84 years	3	3	
Gender categorical Units: Subjects			
Female	25	25	
Male	42	42	

End points

End points reporting groups

Reporting group title	TrRaMM4Gy

Reporting group description: -

Primary: Primary - progression-free survival

End point title	Primary - progression-free survival[1]

End point description:

Progression events are defined as relapse of disease in patients in CR at the moment of transplant and progressive desease in the others. Relapse is defined according to "WHO diagnostic criteria". Progressive diseases is defined as increasing of 25% of the bulk of disease parameters (blast for leukemia, linfonodes diameters for lymphoma, monoclonal paraprotein in MM).

End point type	Primary

End point timeframe:

Progression-free survival (PFS) within 1 year after transplantation is measured from time of start of HSCT (= day -7) to time of progression event.

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.

End point values	TrRaMM4Gy			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: percent				
median (standard deviation)	43 (± 13)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

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.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	3.0

Reporting groups

Reporting group title	TrRaMM4Gy

Reporting group description: -

Serious adverse events	TrRaMM4Gy		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	TrRaMM4Gy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		
General disorders and administration site conditions			
Hospitalisation	Additional description: • Hospitalisation for diagnostic or regular therapy as provided in the clinical trial plan. It is assumed that patients will be hospitalised at least from day -6 to day +28.		
subjects affected / exposed	26 / 26 (100.00%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2014	Substantial Amendment n.1 of 05-DEC-2014 1) Closure of arms B and C due to problems in enrollment 2) Reduction of sample size 3) Elimination of the pharmacokinetic sub-study "Substudy to evaluate the pharmacokinetics of ATG Fresenius". 4) Review of inclusion / exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported