Clinical trial results:
PARACHUTE-trial

Prospective Analysis of an individualized dosing Regimen of ATG (Thymoglobulin) in Children Undergoing HCT: redUcing Toxicity and improving Efficacy – a single arm phase II study

Summary

EudraCT number	2014-004849-26
Trial protocol	NL
Global end of trial date	31 August 2019
Results information	
Result version number	v1 (current)
This version publication date	19 May 2022
First version publication date	19 May 2022

Trial information

Trial identification	
Sponsor protocol code	NL51460.041.14
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch Competent Authority: NL51460.041.14, Medical Ethical Committee University Medical Cente: 14-672

Notes:

Sponsors	
Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands,
Public contact	R.Admiraal, MD, UMC Utrecht, 0031 0611210706, r.admiraal@umcutrecht.nl
Scientific contact	R.Admiraal, MD, UMC Utrecht, 0031 0611210706, r.admiraal@umcutrecht.nl

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	01 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2018
Global end of trial reached?	Yes
Global end of trial date	31 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether an individualized dosing regimen for Thymoglobulin leads to a better immune reconstitution after HCT (definition as in primary endpoint), as compared to historically non-individualized treated patients receiving Thymoglobulin as a fixed dose per kilogram body weight. The individualized dosing regimen is based on a previously treated pediatric cohort on which a population PK-PD analysis was performed. The dosing regimen was compiled using this cohort, taking into account the influence of body weight and pre-Thymoglobulin lymphocyte count and the observed variability.

Protection of trial subjects:

The primary endpoint in the study (early T-cell recovery), potential toxicities associated with the change in therapy (graft-versus-host-disease, graft failure), SAE’s and SUSARs were evaluated by an external data safety monitoring board. Furthermore, the trial was based on a Simon two-stage design which includes an interim efficacy analysis.

Background therapy:

All participants received an allogeneic hematopoietic stem cell transplantation. Conditioning regimens were given according to national and international protocols. Busulfan was targeted with therapeutic drug monitoring (TDM) to reach an area under the curve (AUC) of 75–95 mg × h/day. Patients with severe aplastic anaemia and Fanconi’s anaemia received reduced intensity conditioning. Selective gut decontamination, infection prophylaxis and GvHD prophylaxis was given according to local protocols as described previously11. GvHD prophylaxis consisted of cyclosporin, with TDM to reach trough levels of 150-250 µg/L, combined with methotrexate 10 mg/m2 on day 1, 3 and 6 after infusion (bone marrow) or prednisolone 1mg/kg (cord blood). Patients were treated in high-efficiency, particle-free, air-filtered, positive-pressure isolation rooms. Conditioning regimens (except the ATG dosing), supportive care and transplant team did not change over time (enrolment trial and historical cohort).

Evidence for comparator:

The primary endpoint was CD4+ IR, defined as a CD4+ T-cell count of at least 0·05×10 cells/L at two consecutive measurements within 100±3 days after HCT. Early CD4+ IR was chosen as a primary endpoint, as it was found to be a reliable predictor (in different centres and transplant settings) for transplant outcomes such as survival, NRM, viral reactivations and GvHD.

Actual start date of recruitment	01 April 2015
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	Netherlands: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	10
Children (2-11 years)	34
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Inclusion: pediatric patients receiving an allogeneic hematopoietic cell transplantation in the participating centre from 7-2015 up to 9-2018 in a third-line academic hospital.

Pre-assignment

Screening details:

Patients were enrolled from May 2015 until August 2018 . Patients <18 years receiving their first T-repleted unrelated HCT for any (non)-malignant indication with ATG as part of the conditioning regimen, were eligible. We excluded those not receiving the intended dose of ATG, those who received serotherapy 3 months preceding this HCT; and those not

Period 1

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

Blinding implementation details:

NA

Arms

Arm title	Intervention arm

Arm description:

Individualized dosing of anti-thymocyte globulin

Arm type	Experimental
Investigational medicinal product name	Thymoglobulin
Investigational medicinal product code	
Other name	Anti-thymocyte globulin
Pharmaceutical forms	Powder and solution for suspension for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

Cumulative dose of 2-10 mg/kg over 1-4 days depending on body weight, lymphocyte counts before the first dose and the stem cell source. Thymoglobulin was infused as a daily 4-hour infusion.

Number of subjects in period 1	Intervention arm
Started	64
Completed	58
Not completed	6
Adverse event, serious fatal	2
Adverse event, non-fatal	2
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	64	64	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	20	20	
Children (2-11 years)	34	34	
Adolescents (12-17 years)	10	10	
Age continuous Units: years			
median	7.4		
full range (min-max)	0.2 to 17.4	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	32	32	

Subject analysis sets	
Subject analysis set title	Efficacy-Evaluable Population
Subject analysis set type	Per protocol

Subject analysis set description:

All- Treated population minus patients having events (death, relapse, graft failure) before 100 days

Subject analysis set title	All-Treated population
Subject analysis set type	Per protocol

Subject analysis set description:

All included patients minus those with major protocol deviations, and those not receiving the full dose of Thymoglobulin

Reporting group values	Efficacy-Evaluable Population	All-Treated population	
Number of subjects	51	58	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Age continuous Units: years			
median	7.4	7.4	
full range (min-max)	0.2 to 17.8	0.2 to 17.8	

Gender categorical Units: Subjects			
Female	29	29	
Male	29	29	

End points

End points reporting groups

Reporting group title	Intervention arm
Reporting group description: Individualized dosing of anti-thymocyte globulin	
Subject analysis set title	Efficacy-Evaluable Population
Subject analysis set type	Per protocol
Subject analysis set description: All- Treated population minus patients having events (death, relapse, graft failure) before 100 days	
Subject analysis set title	All-Treated population
Subject analysis set type	Per protocol
Subject analysis set description: All included patients minus those with major protocol deviations, and those not receiving the full dose of Thymoglobulin	

Primary: Successful CD4+ T-cell reconstitution

End point title	Successful CD4+ T-cell reconstitution[1]
End point description: Reaching a CD4+ T-cell count >50 twice within 100 days after transplantation	
End point type	Primary
End point timeframe: Within 100 days after stem cell transplantation	

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: We performed a Simon 2-stage analysis in the trial, as described in the protocol and manuscript. As the EudraCT-system would not allow us to describe the results of the single-arm statistical test, we could not upload the results of the analysis.

End point values	Efficacy-Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Patients	41			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

7-2015 up to 9-2019

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.3

Reporting groups

Reporting group title	All included patients

Reporting group description:

All patients included in the study, also including major protocol violations

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: There were no non-serious adverse events registered in this study, since the treatment at hand is associated with relatively severe adverse events. Registration of non-serious events would have led to too much work.

Serious adverse events	All included patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 64 (23.44%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	15		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukaemia recurrent			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			

subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Allergic reaction to excipient	Additional description: To Thymoglobulin			
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Allergic reaction to excipienttion	Additional description: To liposomal amphoterocin B			
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune pancytopenia	Additional description: Isolated thrombopenia			
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Capillary leak syndrome				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cytokine release syndrome				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Graft loss				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Graft versus host disease				

subjects affected / exposed	5 / 64 (7.81%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	2 / 2			
Immune system disorder				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression	Additional description: Of underlying disease (LICS: lung disease, immunodeficiency, chromosome breakage syndrome)			
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemophagocytic lymphohistiocytosis				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				
Dehydration				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Feeding intolerance				
subjects affected / exposed	4 / 64 (6.25%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhageestinal				
subjects affected / exposed	3 / 64 (4.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Gastrooesophageal reflux diseaseme				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Hyperbilirubinaemia			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Venoocclusive disease			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchiolitis obliterans syndrome			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cystitis viral			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Candida sepsis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheter site infection			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			

subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epstein-Barr viraemia				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	6 / 64 (9.38%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Influenza				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	8 / 64 (12.50%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 1			
Pneumocystis jirovecii pneumoniastis				
subjects affected / exposed	2 / 64 (3.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 2			
Sepsis				
subjects affected / exposed	4 / 64 (6.25%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Skin infection				

subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viralitis			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)		
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	All included patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2015	Addition of second study site (Leiden Academic Medical Center, the Netherlands)
07 March 2016	Additional data for addition of second study site (Leiden Academic Medical Center, the Netherlands)
20 February 2017	Minor protocol changes to the patient information folder, the protocol, addition of contracts with monitor
06 June 2018	Change site to Princess Maxima Center for Pediatric Oncology
22 October 2018	Addition of statistical analysis plan, prolongation of study due to incomplete recruitment
17 December 2018	Change end of study date

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/35114150