



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 Centre: 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 0.05×10⁶ 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 excipient | Additional description: To liposomal amphotericin 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>