# Clinical trial results:
# Prophylaxis of chronic graft-versus-host disease (cGvHD) with or without anti-thymocyte-globulin (ATG) prior allogeneic peripheral stem cell transplantation from HLA-identical siblings after myeloablative conditioning in patients with acute leukemia: a randomized phase III-study

## Summary

| | |
|---|---|
| EudraCT number | 2005-005719-83 |
| Trial protocol | DE IT ES |
| Global end of trial date | 07 May 2014 |
| **Results information** | |
| Result version number | v1 (current) |
| This version publication date | 01 May 2022 |
| First version publication date | 01 May 2022 |
| Summary attachment (see zip file) | Medical journal article (nejmoa1506002-1.pdf)<br>Supplementary (supplmentary ATLG NEJM KROGER BONIFAZI.pdf) |

## Trial information

| **Trial identification** | |
|---|---|
| Sponsor protocol code | ATG Family Study |
| **Additional study identifiers** | |
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

| **Sponsors** | |
|---|---|
| Sponsor organisation name | Department of Stem Cell Transplantation, University Medical Center Eppendorf |
| Sponsor organisation address | Martinistraße, 52, Hamburg, Germany, 20246 |
| Public contact | Francesca Bonifazi, Institute of Hematology and Clinical Oncology "L. and A. Seràgnoli", +39 0512143853, francesca.bonifazi@unibo.it |
| Scientific contact | Nicolaus Kröger, Bone Marrow Transplantation, University Hospital Hamburg-Eppendorf, +49 40428034850, nkroeger@uke.uni-hamburg.de |

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 | 30 June 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate superiority of ATG over Non-ATG in preventing cGvHD after PBSCT, the cumulative incidence of cGvHD in patients with and without ATG administration was compared using competing risk cumulative incidence survival analysis.

Protection of trial subjects:

Insurance coverage for participating patients is provided by the Randomization and Data Management Office through the insurance companies. For Italy: Gerling Konzern

Background therapy:

Standard GVHD prohylaxis was with Cyclosporine and Methotrexate; the study added in the experimental arm ATG Fresenius, administered ad doses of 10 mg/kg BW on days -3, -2, and -1 before PBSCT via central venous catheter (total cumulative dose: 30 mg/kg BW)

Evidence for comparator:

Cyclosporineand Methotrexate (comparator) was considered the standard option in the EBMT-ELN recommendation (Ruutu T. et al. – Bone Marrow Transplantation 2013)

| | |
|---|---|
| Actual start date of recruitment | 16 November 2006 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 21 |
| Country: Number of subjects enrolled | Germany: 31 |
| Country: Number of subjects enrolled | Italy: 99 |
| Country: Number of subjects enrolled | Israel: 10 |
| Worldwide total number of subjects | 161 |
| EEA total number of subjects | 151 |

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) | 161 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Male and female patients, 18 – 65 years of age, suffering from ALL or AML in complete remission. Availability of an HLA-identical sibling as a peripheral blood stem cell donor.

### Pre-assignment

Screening details:

Patients with left ventricular ejection fraction < 30 %, Total bilirubin, SGPT or SGOT > 5 times upper the normal level, Creatinine clearance < 30 ml/min, DLCO < 35 % and/or receiving supplementary continuous oxygen.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 161 |
| Number of subjects completed | 161 |

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Treatment with ATG |

Arm description:

Experimental arm adding ATG to the standard GVHD prophylaxis with CSA and MTX

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ATG Fresenius |
| Investigational medicinal product code | L04AA03 |
| Other name | ANTI-HUMAN – T – LINPHCYTE IMMUNOGLOBULIN SERUM CONCENTRATE |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Administered ad doses of 10 mg/kg BW on days -3, -2, and -1 before PBSC transplant (total cumulative dose: 30 mg/kg BW)

| | |
|---|---|
| Investigational medicinal product name | Busilvex/Busulfan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Busulfan was given at a total dose of 16 mg/kg BW orally or in form of Busilvex® at a dose of 12.8 mg/kg intravenously and it was administered from day -9 to day -6 at a dose of 4 mg/kg BW (orally) or 3.2 mg/kg BW (intravenously) per day. The preferred application of busulfan, however, was Busilvex® intravenously. Busilvex® was administered intravenously via a central venous catheter. The dose of Busilvex® was 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered as a two hour infusion every six hours for four days for a total of 16 doses, starting on day -9 to day -6. For obesive or severely obesive patients Busilvex® was administered based on adjusted ideal body weight.

| | |
|---|---|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cyclophosphamide at a dose of 120 mg/kg body weight was given intravenously via a central venous catheter on day -4 and -3 at 60 mg/kg BW per day for a total dose of 120 mg/kg BW.

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

Dosage and administration details:

Mesna to prevent hemorrhagic cystitis was used according to the local practice.

| | |
|---|---|
| Investigational medicinal product name | VP-16 (Etoposide) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Etoposide (VP-16) was given to TBI/Cyclophosphamide or Busulfan/Cyclophosphamide at a dose of 30 - 45 mg/kg, which were given intravenously.

| | |
|---|---|
| Investigational medicinal product name | Cyclosporine A |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Cyclosporine A was started at a dose of 3 mg/kg BW per day as continuous infusion, starting on day -1, according to the local standard policy. Cyclosporine A was switched orally, 3 mg/kg b.i.d. when tolerating oral medications, in the absence of GvHD.

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

Dosage and administration details:

Methotrexate was given on day 1 at a dose of 15 mg/m², and at a dose of 10 mg/m² on day 3, day 6, and day 11 intravenously. In case of severe mucositis and high bilirubin level the dose of methotrexate was adjusted according to the local policy.

| | |
|---|---|
| **Arm title** | Non ATG |

Arm description:

Standard arm where patients received the standard GVHD prophylaxis with CSA and MTX

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Busilvex/Busulfan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Busulfan was given at a total dose of 16 mg/kg BW orally or in form of Busilvex® at a dose of 12.8 mg/kg intravenously and it was administered from day -9 to day -6 at a dose of 4 mg/kg BW (orally) or

3.2 mg/kg BW (intravenously) per day. The preferred application of busulfan, however, was Busilvex® intravenously. Busilvex® was administered intravenously via a central venous catheter. The dose of Busilvex® was 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered as a two hour infusion every six hours for four days for a total of 16 doses, starting on day -9 to day -6. For obesive or severely obesive patients Busilvex® was administered based on adjusted ideal body weight.

| | |
|---|---|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cyclophosphamide at a dose of 120 mg/kg body weight was given intravenously via a central venous catheter on day -4 and -3 at 60 mg/kg BW per day for a total dose of 120 mg/kg BW.

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

Dosage and administration details:

Mesna to prevent hemorrhagic cystitis was used according to the local practice.

| | |
|---|---|
| Investigational medicinal product name | VP-16 (Etoposide) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Etoposide (VP-16) was given to TBI/Cyclophosphamide or Busulfan/Cyclophosphamide at a dose of 30 - 45 mg/kg, which were given intravenously.

| | |
|---|---|
| Investigational medicinal product name | Cyclosporine A |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Cyclosporine A was started at a dose of 3 mg/kg BW per day as continuous infusion, starting on day -1, according to the local standard policy. Cyclosporine A was switched orally, 3 mg/kg b.i.d. when tolerating oral medications, in the absence of GvHD.

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

Dosage and administration details:

Methotrexate was given on day 1 at a dose of 15 mg/m², and at a dose of 10 mg/m² on day 3, day 6, and day 11 intravenously. In case of severe mucositis and high bilirubin level the dose of methotrexate was adjusted according to the local policy.

| **Number of subjects in period 1** | Treatment with ATG | Non ATG |
|---|---|---|
| Started | 86 | 75 |
| Completed | 83 | 72 |
| Not completed | 3 | 3 |
| Leukemia relapse | 3 | 1 |
| Consent withdrawn by donor | - | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Treatment with ATG |
| Reporting group description: | |
| Experimental arm adding ATG to the standard GVHD prophylaxis with CSA and MTX | |
| Reporting group title | Non ATG |
| Reporting group description: | |
| Standard arm where patients received the standard GVHD prophylaxis with CSA and MTX | |

| Reporting group values | Treatment with ATG | Non ATG | Total |
|---|---|---|---|
| Number of subjects | 86 | 75 | 161 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 86 | 75 | 161 |
| Age continuous<br>Units: years | | | |
| median | 39 | 43.5 | |
| full range (min-max) | 18 to 64 | 21 to 61 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 32 | 33 | 65 |
| Male | 54 | 42 | 96 |
| Baseline Characteristics of the Participiants<br>Units: Subjects | | | |
| First complete remission at transplantation | 73 | 66 | 139 |
| Second complete remission at transplantation | 10 | 6 | 16 |
| Excluded patients | 3 | 3 | 6 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Randomized and treated patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Randomized and treated patients | |

| Reporting group values | Randomized and treated patients | | |
|---|---|---|---|
| Number of subjects | 155 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 155 | | |
| Age continuous<br>Units: years | | | |
| median | 41.25 | | |
| full range (min-max) | 18 to 64 | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 62 | | |
| Male | 93 | | |
| Baseline Characteristics of the Participants<br>Units: Subjects | | | |
| First complete remission at transplantation | 139 | | |
| Second complete remission at transplantation | 16 | | |
| Excluded patients | 0 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Treatment with ATG |
| Reporting group description: | |
| Experimental arm adding ATG to the standard GVHD prophylaxis with CSA and MTX | |
| Reporting group title | Non ATG |
| Reporting group description: | |
| Standard arm where patients received the standard GVHD prophylaxis with CSA and MTX | |
| Subject analysis set title | Randomized and treated patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Randomized and treated patients | |

### Primary: Cumulative Incidence of cGVHD

| | |
|---|---|
| End point title | Cumulative Incidence of cGVHD |
| End point description: | |
| Comparison of cumulative incidence of chronic GvHD (limited or extensive) after allogeneic peripheral blood stem cell transplantation from HLA-identical siblings with or without antithymocyte globulin according to the revised Seattle criteria of Lee et al. | |
| End point type | Primary |
| End point timeframe: | |
| The primary endpoint of the study was the cumulative incidence of chronic GVHD at 2 years. | |

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 24 | 9 | | |

### Statistical analyses

| Statistical analysis title | Cumulative incidence analyses |
|---|---|
| Statistical analysis description: | |
| Cumulative incidence analyses were performed with the use of NCSS statistical software, version 9, and R statistical software, version 2.10.1 (cmprsk package) | |
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

| Secondary: Relapse | |
|---|---|
| End point title | Relapse |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 33 | 35 | | |

**Statistical analyses**

| Statistical analysis title | Relapse analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

| Secondary: Relapse-free Survival | |
|---|---|
| End point title | Relapse-free Survival |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 33 | 35 | | |

**Statistical analyses**

| **Statistical analysis title** | Relapse-free Survival analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

**Secondary: Overall Survival**

| End point title | Overall Survival |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| **End point values** | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 36 | 35 | | |

**Statistical analyses**

| **Statistical analysis title** | Overall Survival analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

**Secondary: Non relapse-Related Death**

| End point title | Non relapse-Related Death |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| 2 years | |

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 36 | 36 | | |

**Statistical analyses**

| Statistical analysis title | Non relapse-Related Death |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Chi-squared |

**Secondary: Chronic GVHD–free + Relapse free Survival**

| End point title | Chronic GVHD–free + Relapse free Survival |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

2 years

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 22 | 8 | | |

**Statistical analyses**

| Statistical analysis title | Chronic GVHD–free + Relapse free Survival |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |

| | |
|---|---|
| Number of subjects included in analysis | 155 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

## Secondary: Leucocytes engrafment

| | |
|---|---|
| End point title | Leucocytes engrafment |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

2 years

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: days | | | | |
| median (full range (min-max)) | 18 (10 to 31) | 15 (11 to 34) | | |

### Statistical analyses

| Statistical analysis title | Leucocytes engrafment analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Platelet engrafment

| | |
|---|---|
| End point title | Platelet engrafment |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

2 years

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: days | | | | |
| median (full range (min-max)) | 20 (10 to 110) | 13 (6 to 29) | | |

**Statistical analyses**

| Statistical analysis title | Platelet engrafment analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Acute GVHD**

| End point title | Acute GVHD |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

100 days

| End point values | Treatment with ATG | Non ATG | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 72 | | |
| Units: Patients | 21 | 25 | | |

**Statistical analyses**

| Statistical analysis title | Acute GVHD analysis |
|---|---|
| Comparison groups | Treatment with ATG v Non ATG |
| Number of subjects included in analysis | 155 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Regression, Cox |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Report period (any causal relationship to ATG-Fresenius S), by MedDRA System Organ Classes and Preferred Terms (all randomized patients).

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 8.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Treatment with ATG |

Reporting group description:

Randomized and allocated in experimental arm where patients have been treated adding ATG to the standard GVHD prophylaxis with CSA and MTX

| | |
|---|---|
| Reporting group title | NON-ATG |

Reporting group description:

Randomized, treated and allocated to comparator arm where patients received the standard GVHD prophylaxis with CSA and MTX

| Serious adverse events | Treatment with ATG | NON-ATG | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 83 (9.64%) | 4 / 72 (5.56%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Leukaemia recurrent | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 1 / 72 (1.39%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myeloid leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Mastectomy | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 72 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 72 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Myelitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 72 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 72 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 72 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 4.77 %

| **Non-serious adverse events** | Treatment with ATG | NON-ATG | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 83 (73.49%) | 72 / 72 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 0 / 72 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Vascular disorders | | | |
| Vascular disorders | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 5 / 72 (6.94%) | |
| occurrences (all) | 1 | 7 | |
| General disorders and administration site conditions | | | |
| General disorders and administration site conditions | | | |
| subjects affected / exposed | 6 / 83 (7.23%) | 13 / 72 (18.06%) | |
| occurrences (all) | 7 | 21 | |
| Immune system disorders | | | |
| Immune system disorders | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 3 / 72 (4.17%) | |
| occurrences (all) | 3 | 3 | |
| Reproductive system and breast disorders | | | |
| Reproductive system and breast disorders | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 4 / 72 (5.56%) | |
| occurrences (all) | 4 | 7 | |
| Psychiatric disorders | | | |
| Psychiatric disorders | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Investigations | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 72 (2.78%) | |
| occurrences (all) | 0 | 8 | |
| Injury, poisoning and procedural complications | | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 83 (1.20%) | 1 / 72 (1.39%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac disorders | | | |
| Cardiac disorders | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 6 / 72 (8.33%) | |
| occurrences (all) | 1 | 6 | |
| Nervous system disorders | | | |
| Nervous system disorders | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 4 / 72 (5.56%) | |
| occurrences (all) | 1 | 6 | |
| Blood and lymphatic system disorders | | | |
| Blood and lymphatic system disorders | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 4 / 72 (5.56%) | |
| occurrences (all) | 16 | 6 | |
| Eye disorders | | | |
| Eye disorders | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 9 / 72 (12.50%) | |
| occurrences (all) | 6 | 15 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary disorders | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 72 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and subcutaneous tissue disorders | | | |
| subjects affected / exposed | 10 / 83 (12.05%) | 5 / 72 (6.94%) | |
| occurrences (all) | 12 | 7 | |
| Renal and urinary disorders | | | |
| Renal and urinary disorders | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 4 / 72 (5.56%) | |
| occurrences (all) | 3 | 4 | |
| Endocrine disorders | | | |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 72 (1.39%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal and connective tissue disorders | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 2 / 72 (2.78%) | |
| occurrences (all) | 2 | 3 | |
| Infections and infestations | | | |
| Infections and infestations | | | |
| subjects affected / exposed | 16 / 83 (19.28%) | 14 / 72 (19.44%) | |
| occurrences (all) | 22 | 34 | |
| Metabolism and nutrition disorders | | | |
| Metabolism and nutrition disorders | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 4 / 72 (5.56%) | |
| occurrences (all) | 1 | 8 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported