



Clinical trial results:

Allogeneic hematopoietic cell transplantation with HLA-matched donors : a phase II randomized study comparing 2 nonmyeloablative conditionings

Summary

EudraCT number	2007-002548-12
Trial protocol	BE NL
Global end of trial date	08 July 2016

Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020
Summary attachment (see zip file)	medical journal article (publication.pdf)

Trial information

Trial identification

Sponsor protocol code	TJB0702P1
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00603954
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Liège
Sponsor organisation address	avenue de l'hôpital 1, Liège, Belgium, 4000
Public contact	belgian hematological society, coordinating investigator, 0032 43667201, f.baron@ulg.ac.be
Scientific contact	belgian hematological society, coordinating investigator, 0032 43667201, f.baron@ulg.ac.be

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	15 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2011
Global end of trial reached?	Yes
Global end of trial date	08 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The present project aims at comparing two nonmyeloablative regimens currently used in 2 major transplant centers in the US for patients with HLA-matched related or unrelated donor: the one from the Seattle group consisting of 2 Gy total body irradiation (TBI) with fludarabine (90 mg/m²) versus the one from the Stanford group combining 8 Gy total lymphoid irradiation (TLI) with anti-thymocyte globulin (ATG). The primary objective is to compare the incidence of grade II-IV acute GVHD between the 2 groups.

Protection of trial subjects:

Potential toxicities associated with PBSC infusions will be carefully monitored per the standard procedures.

Background therapy:

After myeloablative conditioning, the association of tacrolimus + methotrexate has been associated with a lower incidence of grade II-IV acute GVHD than the association combining CSP + methotrexate. Based on these observations, we will elect to use tacrolimus instead of CSP in the 2 arms of the current study.

Evidence for comparator:

Associations between GVHD and outcomes after nonmyeloablative HCT: Numerous studies have evinced a close relationship between GVHD and GVT responses after myeloablative HSCT although several observations have demonstrated GVT effects in the absence of GVHD. Thus, even though GVT reactions are thought to be mandatory for eradication of the underlying malignancy after nonmyeloablative conditioning, it has remained unclear whether clinical manifestations of GVHD are required. In order to address this question, we analyzed data from 322 patients given grafts from HLA-matched related (n=192) or unrelated (n=130) donors after 2 Gy TBI with or without fludarabine, and postgrafting immunosuppression with MMF and CSP 21. Time dependent regression Cox models were used to assess the impact of either acute or chronic GVHD on relapse, non-relapse mortality and PFS. In multivariate analyses, grades II and III-IV acute GVHD had no significant impact on the risk of relapse/progression, but were associated with an increased risk of non-relapse mortality and decreased progression-free survival (PFS). Conversely, extensive chronic GVHD was associated with a decreased risk of relapse/progression (P = 0.006), and better PFS (P= 0.003).

A novel nonmyeloablative regimen combining total lymphoid irradiation (TLI) with ATG: Based on studies in a murine model, the Stanford group has developed another non-myeloablative regimen that favoured the presence of a high proportion of NK-T regulatory cells, and thus was associated with a low incidence of acute GVHD. This regimen consists of total lymphoid irradiation (TLI; 8 Gy) and ATG (Thymoglobulin, 7.5 mg/kg total dose), and postgrafting immunosuppression with MMF and CSP. First results in 37 patients indicated that this regimen was indeed associated with a low incidence of grade II-IV acute GVHD (1 of 37 patients) despite a high rate of stable engraftment, while graft-versus-tumor effects were apparently preserved. In a recent u

Actual start date of recruitment	02 January 2008
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	Netherlands: 7
Country: Number of subjects enrolled	Belgium: 100
Worldwide total number of subjects	107
EEA total number of subjects	107

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)	80
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from January 2008 to March 2011 in the participating centers.

107 patients included, but 94 evaluable patients because screening failure (10 before transplantation and 3 excluded of analysis)

Pre-assignment

Screening details:

13 patients (6 in the Flu-TBI and 7 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse (5), ineligible for further irradiation (3), donor refusal to give PBSC (2) HLA-mismatched donor (2), and poor PS (1))

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TBI arm

Arm description:

In the TBI arm, conditioning will consist of fludarabine 30 mg/m² on days -4, -3 and -2 (total dose 90 mg/m²), followed by a single dose of 2 Gy TBI administered on day 0, at a low dose-rate (\approx 7 cGy/min), before infusion of cells

Arm type	Active comparator
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

fludarabine 30 mg/m² infused on days -4, -3 and -2 (total dose 90 mg/m²)

Arm title	TLI arm
------------------	---------

Arm description:

In the TLI arm, conditioning will consist of 8 Gy TLI and ATG. TLI will be administered by linear accelerator at a dose of 80 cGy daily, starting 11 days before transplantation, until a total of 10 doses (800 cGy) has been delivered. The irradiation will consist of a supradiaphragmatic mantle field, a subdiaphragmatic field including an inverted Y and splenic ports, encompassing all major lymphoid organs, including the thymus, spleen, and lymph nodes, as used in the treatment of Hodgkin's disease (Kaplan HS, Cancer Research 26:1268-1276, 1966). The Waldeyer ring is not included. ATG (Thymoglobulin®, Genzyme), at a dose of 1.5 mg/kg/d, will be given intravenously on days -11 through -7.

Arm type	Active comparator
Investigational medicinal product name	Thymoglobuline
Investigational medicinal product code	
Other name	ATG
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ATG (Thymoglobulin®, Genzyme) infused intravenously at a dose of 1.5 mg/kg/d on days -11 through -7 (total dose 7.5 mg/kg)

Number of subjects in period 1 ^[1]	TBI arm	TLI arm
Started	49	45
Completed	49	45

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 13/107 included patients (6 in the Flu-TBI and 7 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n = 5), ineligible for further irradiation (n = 3), donor refusal to give peripheral blood stem cells (PBSC) (n = 2), HLA-mismatched donor (n = 2), and poor PS precluding transplantation (n = 1)). the analysis includes data from 94 patients.

Baseline characteristics

Reporting groups

Reporting group title	overall trial
-----------------------	---------------

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	94	94	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	58		
full range (min-max)	32 to 73	-	
Gender categorical			
Units: Subjects			
Female	30	30	
Male	64	64	
Donor type			
Units: Subjects			
HLA-identical sibling	54	54	
10/10 HLA-allele matched URD	40	40	
CMV-serostatus (donor/patient)			
the CMV serostatus of one recipient (CMV sero-positive donor) is missing; the CMV serostatus of one recipient (CMV sero-negative donor) is missing;			
Units: Subjects			
-/-	25	25	
-/+	29	29	
+/-	11	11	
+/+	27	27	
unknown	2	2	
Disease at transplantation;			
Units: Subjects			
Acute myeloid leukemia	33	33	
Acute lymphoblastic leukemia	5	5	
Chronic lymphocytic leukemia	10	10	
Myelodysplastic syndrome	17	17	
Chronic myelomonocytic leukemia	5	5	
Multiple myeloma	5	5	

Myeloproliferative disorder	3	3	
Non-Hodgkin lymphoma	15	15	
Waldenström disease	1	1	
Disease risk			
Units: Subjects			
low	27	27	
standard	42	42	
high	25	25	

Subject analysis sets

Subject analysis set title	Evaluable patient TBI arm
Subject analysis set type	Full analysis

Subject analysis set description:

94 patients on 107 patients included were analysed. Thirteen patients (6 in the Flu-TBI and 7 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n = 5), ineligible for further irradiation (n = 3), donor refusal to give peripheral blood stem cells (PBSC) (n = 2), HLA-mismatched donor (n = 2), and poor PS precluding transplantation (n = 1)).

Subject analysis set title	Evaluable patient TLI arm
Subject analysis set type	Full analysis

Subject analysis set description:

13/107 patients (6/55 in the Flu-TBI and 7/52 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n = 5), ineligible for further irradiation (n = 3), donor refusal to give peripheral blood stem cells (PBSC) (n = 2), HLA-mismatched donor (n = 2), and poor PS precluding transplantation (n = 1))

Reporting group values	Evaluable patient TBI arm	Evaluable patient TLI arm	
Number of subjects	49	45	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	60	59	
full range (min-max)	38 to 73	32 to 71	
Gender categorical			
Units: Subjects			
Female	14	16	
Male	35	29	

Donor type			
Units: Subjects			
HLA-identical sibling	29	25	
10/10 HLA-allele matched URD	20	20	
CMV-serostatus (donor/patient)			
the CMV serostatus of one recipient (CMV sero-positive donor) is missing; the CMV serostatus of one recipient (CMV sero-negative donor) is missing;			
Units: Subjects			
-/-	12	13	
-/+	17	12	
+/-	8	3	
+/+	11	16	
unknown	1	1	
Disease at transplantation;			
Units: Subjects			
Acute myeloid leukemia	17	16	
Acute lymphoblastic leukemia	4	1	
Chronic lymphocytic leukemia	7	3	
Myelodysplastic syndrome	9	8	
Chronic myelomonocytic leukemia	2	3	
Multiple myeloma	3	2	
Myeloproliferative disorder	2	1	
Non-Hodgkin lymphoma	5	10	
Waldenström disease	0	1	
Disease risk			
Units: Subjects			
low	15	12	
standard	24	18	
high	10	15	

End points

End points reporting groups

Reporting group title	TBI arm
-----------------------	---------

Reporting group description:

In the TBI arm, conditioning will consist of fludarabine 30 mg/m² on days -4, -3 and -2 (total dose 90 mg/m²), followed by a single dose of 2 Gy TBI administered on day 0, at a low dose-rate (≈ 7 cGy/min), before infusion of cells

Reporting group title	TLI arm
-----------------------	---------

Reporting group description:

In the TLI arm, conditioning will consist of 8 Gy TLI and ATG. TLI will be administered by linear accelerator at a dose of 80 cGy daily, starting 11 days before transplantation, until a total of 10 doses (800 cGy) has been delivered. The irradiation will consist of a supradiaphragmatic mantle field, a subdiaphragmatic field including an inverted Y and splenic ports, encompassing all major lymphoid organs, including the thymus, spleen, and lymph nodes, as used in the treatment of Hodgkin's disease (Kaplan HS, Cancer Research 26:1268-1276, 1966). The Waldeyer ring is not included. ATG (Thymoglobulin®, Genzyme), at a dose of 1.5 mg/kg/d, will be given intravenously on days -11 through -7.

Subject analysis set title	Evaluable patient TBI arm
----------------------------	---------------------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

94 patients on 107 patients included were analysed. Thirteen patients (6 in the Flu-TBI and 7 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n = 5), ineligible for further irradiation (n = 3), donor refusal to give peripheral blood stem cells (PBSC) (n = 2), HLA-mismatched donor (n = 2), and poor PS precluding transplantation (n = 1)).

Subject analysis set title	Evaluable patient TLI arm
----------------------------	---------------------------

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

13/107 patients (6/55 in the Flu-TBI and 7/52 in the TLI-ATG arm) were excluded from analysis because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n = 5), ineligible for further irradiation (n = 3), donor refusal to give peripheral blood stem cells (PBSC) (n = 2), HLA-mismatched donor (n = 2), and poor PS precluding transplantation (n = 1))

Primary: The 180-day incidence of grade II-IV acute GVHD

End point title	The 180-day incidence of grade II-IV acute GVHD
-----------------	---

End point description:

The similar incidence of acute GVHD in the 2 arms was due to a lower than anticipated incidence of grade II-IV acute GVHD in the TBI arm, perhaps due to a relatively high dose of MMF used in sibling recipients, and to the relatively high targeted tacrolimus levels the first 100 days after transplantation.

End point type	Primary
----------------	---------

End point timeframe:

Incidence of grade II-IV acute GVHD at D180 after transplantation

End point values	TBI arm	TLI arm	Evaluable patient TBI arm	Evaluable patient TLI arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	49	45	48 ^[1]	40 ^[2]
Units: number	48	40	48	40

Notes:

[1] - Patients given a second allogeneic HCT were censored for GVHD analyses.

[2] - Patients given a second allogeneic HCT were censored for GVHD analyses.

Attachments (see zip file)	Fig3 Transplant outcomes A) D180 gd2-4 aGVHD/Figure3.png
-----------------------------------	--

Statistical analyses

Statistical analysis title	Incidence of grade II-IV acute GVH
Statistical analysis description: The 180-day cumulative incidences of grade II-IV acute GVHD were 12.2% versus 8.9% in Flu-TBI and TLI ATG patients, respectively. Patients given a second allogeneic HCT were censored for GVHD analyses.	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.508 ^[3]
Method	Multivariate Cox models

Notes:

[3] - The similar incidence of acute GVHD in the 2 arms

Secondary: hematopoietic (whole blood and T-cell chimerisms) engraftment and incidence of graft rejection

End point title	hematopoietic (whole blood and T-cell chimerisms) engraftment and incidence of graft rejection
End point description: Determination of Graft failure T-cell chimerism BM chimerism ANC absolute neutrophils count (cells/ μ L) ALC absolute lymphocytes count (cells/ μ L) RBC Red blood cell count (Hemoglobin g/dL) Platelet count (g/dL) + number/timing of transfusions (plt and RBD)	
End point type	Secondary
End point timeframe: 1 year after transplatation	

End point values	Evaluable patient TBI arm	Evaluable patient TLI arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	45		
Units: number	49	45		

Attachments (see zip file)	Fig2 Chimerism levels A) Tcell B) BM chimerism/Figure2.png Hematological recovery/Figure1.png
-----------------------------------	--

Statistical analyses

Statistical analysis title	Hematopoietic engraftment: Donor T-cell chimerism
-----------------------------------	---

Statistical analysis description:

Donor T-cell chimerism levels were lower in the TLI ATG arm on days 180 and 365 after HCT

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.002 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - See Figure 2 chimerism levels (A)

[5] - T cell chimerism levels: P=0.09 at D100, P=0.02 at D180 and P=0.002 at D365

Statistical analysis title	Graft rejection
-----------------------------------	-----------------

Statistical analysis description:

3 patients in the Flu-TBI arm and 4 patients in the TLI-ATG arm had graft rejection (defined as $\leq 5\%$ donor chimerism in T cells, total white blood cells and/or total bone marrow cells).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Hematopoietic engraftment: marrow chimerism
-----------------------------------	---

Statistical analysis description:

TLI-ATG patients had lower marrow chimerism levels on days 40 and 180 after allo-HCT.

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.03 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - See Figure 2 chimerism levels (B)

[7] - Bone marrow (BM) chimerism levels: P=0.03 at D40 and P=0.01 at D180

Statistical analysis title	Hematologic recovery: ANC count
-----------------------------------	---------------------------------

Statistical analysis description:

In comparison to Flu-TBI patients, TLI-ATG patients had significantly lower absolute neutrophil counts on day 0

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
-------------------	---

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Day 0

Statistical analysis title	Hematologic recovery: ALC count
-----------------------------------	---------------------------------

Statistical analysis description:

In comparison to Flu-TBI patients, TLI-ATG patients had significantly lower absolute lymphocyte counts from day 0 to day 42 after transplantation (Fig 1B).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Day 0, 7, 14, 21 < 0.001, D28= 0.01, D42= 0.04

Statistical analysis title	Hematologic recovery: Hemoglobin levels
-----------------------------------	---

Statistical analysis description:

In comparison to Flu-TBI patients, TLI-ATG patients had significantly lower hemoglobin levels on day 0 and from day 21 to day 180 after transplantation (Fig1C).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - P values at Day 0 =0.006, D21 < 0.001, D28 = 0.03, D42= 0.003, D60=0.01, D100=0.03, D180=0.02

Statistical analysis title	Hematologic recovery: platelet levels
-----------------------------------	---------------------------------------

Statistical analysis description:

In comparison to Flu-TBI patients, TLI-ATG patients had significantly lower platelet counts on days 0 and 7 after transplantation (Fig 1d)

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Day 0 < 0.001 and Day 7< 0.001

Statistical analysis title	Hematologic recovery: RBC transfusion
-----------------------------------	---------------------------------------

Statistical analysis description:

Accordingly, 30 of 49 Flu-TBI patients versus 38 of 45 TLI-ATG patients were given at least 1 red blood

cell transfusion the first 100 days after transplantation (P = 0.02) during that period.

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Hematologic recovery: platelet transfusion
-----------------------------------	--

Statistical analysis description:

Accordingly, 14 of 49 Flu-TBI patients versus 26 of 45 TLI-ATG patients were given at least 1 platelet transfusion during that period (P = 0.006).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of chronic GVHD

End point title	Incidence of chronic GVHD
-----------------	---------------------------

End point description:

In summary, in comparison to patients included in the Flu-TBI arm, patients included in the TLI-ATG arm had lower incidence of chronic GVHD.

The low incidence of moderate/severe chronic GVHD in TLI-ATG patients is consistent with prior publications from the Stanford group, while the 40% incidence of chronic GVHD in Flu-TBI patients is also in agreement with observation from the Seattle consortium. Although previous studies have demonstrated a lower incidence of chronic GVHD in patients given ATG, the low incidence of chronic GVHD observed in current TLI-ATG recipients is unlikely due to ATG only, given that other studies have demonstrated that median serum active ATG levels the day of transplantation after TLI-ATG regimen are < 5 mg/L, well below the threshold associated with lower incidence of chronic in a recent study by Chawla et al. (8.12 mg/L).

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

End point timeframe:

2 years follow up

End point values	Evaluable patient TBI arm	Evaluable patient TLI arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48 ^[12]	40 ^[13]		
Units: numbers	48	40		

Notes:

[12] - Patients given a second allogeneic HCT were censored for GVHD analyses.

[13] - Patients given a second allogeneic HCT were censored for GVHD analyses.

Attachments (see zip file)	Fig3 Transplant outcomes B) 5yrs mod/severe cGVHD/Figure3.
-----------------------------------	--

Statistical analyses

Statistical analysis title	Incidence of grade II-III of cGVHD
-----------------------------------	------------------------------------

Statistical analysis description:

2-year cumulative incidences of moderate/severe cGVHD were 40.8% versus 17.8% in Flu-TBI and TLI-ATG patients, respectively (P = 0.0165) (Figure 3B).

Patients given a second allogeneic HCT were censored for GVHD analyses.

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.0165
Method	Multivariate Cox models

Notes:

[14] - In multivariate analysis, TLI-ATG conditioning (HR = 0.3, 95% confidence interval (CI): 0.1-0.8, P = 0.010), and transplantation from a HLA-identical sibling donor (HR = 0.5, 95% CI: 0.2-1.0; P = 0.0495) were associated with a lower incidence of moderate/severe cGVHD, while female donor to male recipient was associated with a higher incidence of moderate/severe cGVHD (HR 3.8, 95% CI: 1.7-8.5, P = 0.001).

Secondary: Incidences of infections

End point title	Incidences of infections
-----------------	--------------------------

End point description:

Comparison of the number of patients who developed at least one infectious episode in the 2 groups was performed using the Fisher's exact test.

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

End point timeframe:

1 year after transplantation

End point values	Evaluable patient TBI arm	Evaluable patient TLI arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	45		
Units: number	49	45		

Attachments (see zip file)	Fig3 Transplant outcomes. C) D100 CMV reactivation/Figure3.
-----------------------------------	---

Statistical analyses

Statistical analysis title	Bacterial infection
-----------------------------------	---------------------

Statistical analysis description:

Nineteen of 49 Flu-TBI patients (39%) versus 25 of 45 TLI ATG patients (56%) had a least one episode of bacterial infection the first 100 days after transplantation (P = 0.15).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
-------------------	---

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Fisher exact

Statistical analysis title	Fungal infection
Statistical analysis description: For fungal infections, the figures were 3 of 45 (6%) and 7 of 45 (16%), respectively (P = 0.19)	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Fisher exact

Statistical analysis title	CMV infection
Statistical analysis description: Among CMV-seropositive patients and/or donors, the 100-day cumulative incidence of CMV reactivation was 31% in Flu-TBI patients versus 47% in TLI-ATG patients (P = 0.12;Figure 3C).	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Secondary: Incidence of relapse (RI), nonrelapse mortality (NRM), progressionfree survival (PFS) and overall survival (OS)

End point title	Incidence of relapse (RI), nonrelapse mortality (NRM), progressionfree survival (PFS) and overall survival (OS)
-----------------	---

End point description:

In summary, in comparison to patients included in the Flu-TBI arm, patients included in the TLI-ATG arm had higher incidence of relapse and similar OS. The TLI-ATG regimen was also associated with a higher incidence of relapse, although these results should be taken with caution given the heterogeneity of diagnoses and status at transplantation in our study. Nevertheless, supporting our data, the incidence of relapse in TLI-ATG patients in the current study (50% at 4 years) is comparable to what has been observed by the Stanford group (53% at 4-year) in a larger cohort of patients. This observation is also in accordance with prior studies that observed higher risks of relapse with lower donor T-cell chimerism and absence of chronic GVHD. This higher incidence of relapse in TLI-ATG patients translated into a trend for lower PFS, but, importantly, OS was identical in the 2 arms.

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

End point timeframe:

4 and 5 years follow up after transplantation

End point values	Evaluable patient TBI arm	Evaluable patient TLI arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	45		
Units: number	49	45		

Attachments (see zip file)	Fig3 Transplant outcomes. 5yrs D) RI E)PFS F)OS/Figure3.png Table 2 Causes of death/Table2.png
-----------------------------------	---

Statistical analyses

Statistical analysis title	Incidence of relapse (RI)/progression
<p>Statistical analysis description:</p> <p>Four-year cumulative incidences of relapse/progression were 22% and 50% in Flu-TBI and TLI-ATG patients, respectively (P = 0.017; Figure 3D). The difference remained statistically significant in multivariate analysis (HR = 2.3, 95% CI 1.1-4.7, P = 0.02).</p>	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.017 ^[16]
Method	Multivariate Cox models
Parameter estimate	Hazard ratio (HR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	4.7

Notes:

[15] - Cumulative incidence curves were used for relapse incidences (RI) with death as a competitive risk

[16] - statistically significant

Statistical analysis title	Incidence of nonrelapse mortality (NMR)
<p>Statistical analysis description:</p> <p>Four-year cumulative incidences of NRM were 24% and 13% in Flu-TBI and TLI-ATG patients, respectively (P = 0.5).</p>	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.5
Method	Cumulative incidence

Notes:

[17] - Cumulative incidence curves with relapse as a competitive risk

Statistical analysis title	Progression Free Survival (PFS)
-----------------------------------	---------------------------------

Statistical analysis description:

4-year PFS was 54% in the Flu-TBI arm, versus 37% (P = 0.12) in the TLI-ATG arm.

5-year PFS was 50% in Flu-TBI patients, versus 37% (P = 0.14) in TLI-ATG patients.

Median follow-up for surviving patients of 58.5 months.

(Figure 3 E-F)

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.14 ^[19]
Method	Kaplan-Meier method
Parameter estimate	Hazard ratio (HR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.1

Notes:

[18] - In multivariate analyses, there was a trend for lower PFS in patients transplanted for high-risk disease (HR = 2.0, 95% CI: 1.0-4.1, P = 0.07), while higher HCT-CI scores predicted for lower OS (HR = 1.2, 95% CI: 1.0-1.4, P = 0.02).

[19] - 4-year P=0.12 and 5-year P=0.14

Statistical analysis title	Overall Survival (OS)
-----------------------------------	-----------------------

Statistical analysis description:

4-year OS was 53% in the TBI arm, versus 54% (P = 0.9) in the TLI-ATG arm.

5-year OS was 53% in Flu-TBI patients, versus 55% (P = 0.96) in TLI-ATG patients.

Median follow-up for surviving patients of 58.5 months.

Figure 3 E-F

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.96 ^[21]
Method	Kaplan-Meier method
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.4

Notes:

[20] - In multivariate analyses, there was a trend for lower PFS in patients transplanted for high-risk disease (HR = 2.0, 95% CI: 1.0-4.1, P = 0.07), while higher HCT-CI scores predicted for lower OS (HR = 1.2, 95% CI: 1.0-1.4, P = 0.02).

[21] - 4-year P=0.9 and 5-year P=0.96

Secondary: Quality and timing of immunologic reconstitution

End point title	Quality and timing of immunologic reconstitution
End point description:	
1. cytokine levels	
2. T-cell chimerism levels and immune recovery	
3. Lymphocyte subset reconstitutions:	
- CD8+ and CD4+ lymphocyte subsets	
- Treg and NK/T-cell recovery	
- B- and NK cell subset recovery	
4. Thymic function (sjTREC levels)	
End point type	Secondary
End point timeframe:	
During 3 or 4 years after the transplantation	

End point values	Evaluable patient TBI arm	Evaluable patient TLI arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28 ^[22]	25 ^[23]		
Units: cells/microlitre				
number (not applicable)	28	25		

Notes:

[22] - This study includes data from 53 patients (from 4 centers; out of a total cohort of 94 patients)

[23] - This study includes data from 53 patients (from 4 centers; out of a total cohort of 94 patients)

Attachments (see zip file)	TJB0702-TBI Vs TLI -Publication_2015_Hannon_TBIVsTLI.pdf TJB0702-TBI Vs TLI - TJB0702-TBI Vs TLI - TJB0702-TBI Vs TLI -
----------------------------	--

Statistical analyses

Statistical analysis title	Cytokine levels: IL17
Statistical analysis description:	
Fig. 1B, IL7 plasma levels were higher in TLI than in TBI recipients the first 100 days after transplantation, suggesting more pronounced T-cell lymphopenia in TLI recipients, given that IL7 levels after allo-HCT depend mainly on consumption by T cells.	
Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - P values ranged from <0.001 to 0.5

Statistical analysis title	cytokine levels: IL15, IL2, IL4, IL10
-----------------------------------	---------------------------------------

Statistical analysis description:

IL15 levels were comparable between TBI and TLI recipients from preconditioning to day 28, suggesting similar CD8+ T-cell and NK cell recovery in the two groups of patients

IL2 serum levels on D28 were below the threshold for detection (2.1 pg/mL) in the two groups of patients.

IL4 levels were comparable in the 2 arms

IL10 levels were significantly higher in TLI patients (P=0.0481), possibly suggesting a TH-2 polarization of donor T cells or a higher production of IL10 by Treg in TLI arm

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0481 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - IL10 levels were significantly higher in TLI, suggesting a TH-2 polarization of donor T cells or a higher production of IL10 by Treg.

IL4/CD4 cell ratios were significantly higher in TLI (P=0.0004).

Other are comparable (Fig S1A-C Hannon et al.)

Statistical analysis title	cytokine levels: IFNγ & TNFα
-----------------------------------	------------------------------

Statistical analysis description:

IFNγ serum levels were similar between the two groups of patients

TNFα levels were significantly higher in TLI than in TBI patients (P= 0.0493)

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0493 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - TNFα levels were significantly higher in TLI than in TBI patients

Statistical analysis title	Lymphocyte subset reconstitutions: CD8+ & CD4+
-----------------------------------	--

Statistical analysis description:

CD8+ and CD4+ lymphocyte subsets (Hannon et al. Fig. 2): Among CD8+ T cells, TLI patients had lower percentages of naive CD8+ T cells but higher percentages of effector/effector-memory CD8+ T cells (TEM CD8+) than TBI patients. Similar observations were made for CD4+ T cells where TLI patients had dramatically lower percentages of naive CD4+ T cells but higher percentages of effector/effector-memory CD4+ T cells (TEM CD4+).

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
-------------------	---

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - See figure 2 (Hannon et al.)

P< 0.001 for Naive CD4+cell between TLI and TBI at D40 to D180 (Fig 2D).

P< 0.05 for Naive CD8+cell between TLI and TBI at D40 (Fig 2A).

Statistical analysis title	Lymphocyte subset reconstitutions: Treg and NK/T-c
-----------------------------------	--

Statistical analysis description:

Treg and NK/T-cell recovery (Hannon et al. Fig. 3): Given the lower incidence of chronic GVHD observed in TLI patients, study of Treg recovery in our patient population was of particular interest. Median absolute Treg numbers reached the lower limit of normal values 6 months and 2 years after transplantation in TBI and TLI patients, respectively (NS), confirming the previously reported slow Treg recovery after allo-HCT

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - P < 0.001 for ration between Treg/naiveCD4+ T cell (TBI vs TLI) at day 40 and 100, P<0.05 at day 180 and 1year

See Fig 3 A-F (Hannon et al.)

Statistical analysis title	Lymphocyte subset reconstitutions: B- and NK cell
-----------------------------------	---

Statistical analysis description:

B- and NK cell subset recovery:

- B-cell recovery was superimposable in TBI and TLI patients.

- NK cell reconstitution was similar in both arms, with faster recovery of CD56bright NK cells in comparison with CD56dim NK cells, as reported previously by other groups of investigators and particularly after HLA-haploidentical stem cell transplantation.

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Thymic function (sjTREC levels)
-----------------------------------	---------------------------------

Statistical analysis description:

SjTREC levels were significantly higher in TBI than in TLI patients on day 100 as well as 2 and 3 years after transplantation.

Indeed, although median sjTREC levels reached the lower limit of normal 2 years after transplantation in TBI patients, they remained below that limit throughout the study period in those given TLI conditioning. the sjTREC levels increased significantly from D100 to 3 yrs in patients <60yrs and not in >60yrs, reflecting an impaired thymic function in the latter group

Comparison groups	Evaluable patient TBI arm v Evaluable patient TLI arm
-------------------	---

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 ^[29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - sjTREC levels increased significantly from day 100 to 1 year (P=0.027), 2 years (P=0.039), and 3 years (P =0.06) after transplantation in patients < 60 yrs at transplantation, while they did not (P values ranged from 0.11 to 0.6) >=60yrs

Adverse events

Adverse events information

Timeframe for reporting adverse events:

5 years follow up after transplantation

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	3
--------------------	---

Reporting groups

Reporting group title	TBI arm
-----------------------	---------

Reporting group description:

In the TBI arm, conditioning will consist of fludarabine 30 mg/m² on days -4, -3 and -2 (total dose 90 mg/m²), followed by a single dose of 2 Gy TBI administered on day 0, at a low dose-rate (≈ 7 cGy/min), before infusion of cells

Reporting group title	TLI arm
-----------------------	---------

Reporting group description:

In the TLI arm, conditioning will consist of 8 Gy TLI and ATG. TLI will be administered by linear accelerator at a dose of 80 cGy daily, starting 11 days before transplantation, until a total of 10 doses (800 cGy) has been delivered. The irradiation will consist of a supradiaphragmatic mantle field, a subdiaphragmatic field including an inverted Y and splenic ports, encompassing all major lymphoid organs, including the thymus, spleen, and lymph nodes, as used in the treatment of Hodgkin's disease (Kaplan HS, Cancer Research 26:1268-1276, 1966). The Waldeyer ring is not included. ATG (Thymoglobulin®, Genzyme), at a dose of 1.5 mg/kg/d, will be given intravenously on days -11 through -7.

Serious adverse events	TBI arm	TLI arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 49 (83.67%)	41 / 45 (91.11%)	
number of deaths (all causes)	22	19	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Second primary malignancy			
subjects affected / exposed	1 / 49 (2.04%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery	Additional description: Surgery/Intervention (coronary, hip prosthesis, catheter removal, endoscopy biopsy)		

subjects affected / exposed	4 / 49 (8.16%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fever unknown origin	Additional description: FUO, no gem associated/identified		
subjects affected / exposed	3 / 49 (6.12%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired quality of life	Additional description: Impaired general status, weakness		
subjects affected / exposed	2 / 49 (4.08%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	15 / 49 (30.61%)	15 / 45 (33.33%)	
occurrences causally related to treatment / all	0 / 15	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 2	
Chronic graft versus host disease			
subjects affected / exposed	22 / 49 (44.90%)	13 / 45 (28.89%)	
occurrences causally related to treatment / all	0 / 25	0 / 14	
deaths causally related to treatment / all	0 / 2	0 / 0	
Graft loss	Additional description: Graft failure		
subjects affected / exposed	2 / 49 (4.08%)	5 / 45 (11.11%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 49 (4.08%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
neurologic trouble			
	Additional description: sleeping trouble,pain, depression, encephalopathy		
subjects affected / exposed	4 / 49 (8.16%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Relapse			
	Additional description: Relapse/progressive primary hematological disease		
subjects affected / exposed	12 / 49 (24.49%)	22 / 45 (48.89%)	
occurrences causally related to treatment / all	0 / 11	0 / 22	
deaths causally related to treatment / all	0 / 10	0 / 13	
Alveolar hemorrhage			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemolytic Anaemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	

hematuria			
subjects affected / exposed	0 / 49 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
febril neutropenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	3 / 49 (6.12%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett's oesophagus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia	Additional description: Anorexia, complains		
subjects affected / exposed	1 / 49 (2.04%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute renal failure			
subjects affected / exposed	0 / 49 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral resection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
broken ribs			
subjects affected / exposed	0 / 49 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	5 / 49 (10.20%)	5 / 45 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 3	
Lung infection			
subjects affected / exposed	7 / 49 (14.29%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	6 / 49 (12.24%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TBI arm	TLI arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 49 (36.73%)	26 / 45 (57.78%)	
Infections and infestations			
viral CMV reactivation	Additional description: number of first CMV reactivation		
subjects affected / exposed	18 / 49 (36.73%)	21 / 45 (46.67%)	
occurrences (all)	18	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2015	Addition of participating centers (multicentre trial)

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/25652604>

<http://www.ncbi.nlm.nih.gov/pubmed/25779951>