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) 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 Units: Subjects			
Adults (18-64 years)	86	75	161
Age continuous Units: years			
median	39	43.5	
full range (min-max)	18 to 64	21 to 61	-
Gender categorical Units: Subjects			
Female	32	33	65
Male	54	42	96
Baseline Characteristics of the Participiants 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 Units: Subjects			
Adults (18-64 years)	155		
Age continuous Units: years			
median	41.25		
full range (min-max)	18 to 64		

Gender categorical Units: Subjects			
Female	62		
Male	93		
Baseline Characteristics of the Participants 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