Clinical trial results:
A 12-month, multi-center, open-label, randomized, controlled study to evaluate efficacy/safety and evolution of renal function of everolimus in co-exposure with tacrolimus in de novo liver transplant recipients

Summary

EudraCT number	2011-003118-17
Trial protocol	DE
Global end of trial date	08 August 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2018
First version publication date	19 August 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001HDE13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01551212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	08 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that an immunosuppressive regimen based on EVR in co-exposure with TAC has superior efficacy compared to TAC alone on eGFR (Modification of Diet in Renal Disease Study Group-4 (MDRD-4) formula) at Month 12 in de novo liver transplant recipients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

For patients in all groups, corticosteroids were initiated at or prior to the time of transplantation according to local practice. Corticosteroids may have been used for the duration of the study according to the investigator`s discretion, but may not have been eliminated sooner than 6 months post-transplantation.

Evidence for comparator: -

Actual start date of recruitment	24 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 333
Worldwide total number of subjects	333
EEA total number of subjects	333

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)	323
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 642 patients were screened for study eligibility at 15 study centers in Germany. 339 patients were randomized out of which 333 received study treatment and were included in the analyses.

Pre-assignment

Screening details:

Patients were screened for eligibility prior to liver transplantation (LTx). The study treatment started after a run-in period that ended on the day of randomization, scheduled at Day 7-21 post-LTx. Patients may have been initiated on an optional induction therapy, MMF, TAC at investigators' discretion.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus/Tacrolimus

Arm description:

Tacrolimus minimization arm. Everolimus (C0-h: 3-8 ng/mL) + tacrolimus (C0-h: < 5 ng/mL)

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	Certican
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets at dose strengths of 0.25mg, 0.5mg, 0.75mg or 1.0mg in blisters of 10 tablets. Dosing schedule according to blood levels

Arm title	Tacrolimus

Arm description:

Tacrolimus (C0-h: 6-10 ng/ml)

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Tacrolimus Hexal
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets at dose strength of 0.5 mg, 1 mg, or 5 mg

Number of subjects in period 1	Everolimus/Tacrolimus	Tacrolimus
Started	169	164
Full Anylsis Set (FAS)	169	164
Safety Set	169	164
Per Protocol Set (PP)	110 [1]	101 [2]
Completed	166	148
Not completed	3	16
Adverse event, serious fatal	2	4
Consent withdrawn by subject	-	7
Administrative problems	1	2
Graft loss/Retransplantation	-	1
Lost to follow-up	-	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Per Protocol Set (PP) - Randomized, received at least 1 dose of study drug and had no major protocol deviation

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Per Protocol Set (PP) - Randomized, received at least 1 dose of study drug and had no major protocol deviation

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus/Tacrolimus
Reporting group description:	
Tacrolimus minimization arm. Everolimus (C0-h: 3-8 ng/mL) + tacrolimus (C0-h: < 5 ng/mL)	
Reporting group title	Tacrolimus
Reporting group description:	
Tacrolimus (C0-h: 6-10 ng/ml)	

Reporting group values	Everolimus/Tacrolimus	Tacrolimus	Total
Number of subjects	169	164	333
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	166	157	323
From 65-84 years	3	7	10
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.68	53.46	
standard deviation	± 9.38	± 9.64	-
Sex/Gender, Customized Units: Subjects			
Male|	133	121	254
Female|	36	43	79
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	168	157	325
Black|	1	1	2
Asian|	0	3	3
Other|	0	3	3

End points

End points reporting groups	
Reporting group title	Everolimus/Tacrolimus
Reporting group description:	
Tacrolimus minimization arm. Everolimus (C0-h: 3-8 ng/mL) + tacrolimus (C0-h: < 5 ng/mL)	
Reporting group title	Tacrolimus
Reporting group description:	
Tacrolimus (C0-h: 6-10 ng/ml)	

Primary: Estimated glomerular filtration rate (GFR)	
End point title	Estimated glomerular filtration rate (GFR)
End point description:	
The estmated GFR was calculated using MDRD-4 formula (Modification of Diet in Renal Disease Study Group).	
End point type	Primary
End point timeframe:	
month 12	

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: mL/min				
arithmetic mean (standard deviation)	73.46 (± 25.57)	71.95 (± 27.17)		

Statistical analyses

Statistical analysis title	estmated GFR using ANCOVA
Comparison groups	Everolimus/Tacrolimus v Tacrolimus
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.097
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	8.91

Secondary: Estimated GFR - PP Set

End point title	Estimated GFR - PP Set
End point description:	
This was a sensitivity analysis for the primary outcome measure based on the per-protocol set of patients.	
End point type	Secondary
End point timeframe:	
month 12	

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: mL/min				
arithmetic mean (standard deviation)	74.83 (± 25.19)	70.65 (± 24.91)		

Statistical analyses

Statistical analysis title	estmated GFR using ANCOVA
Comparison groups	Everolimus/Tacrolimus v Tacrolimus
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0085
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.06
upper limit	13.92

Secondary: Incidence of composite of treated biopsy proven acute rejection (BPAR), graft loss or death

End point title	Incidence of composite of treated biopsy proven acute rejection (BPAR), graft loss or death
End point description:	
Incidence of composite of treated biopsy proven acute rejection (BPAR), graft loss or death at Month 12	
End point type	Secondary

End point timeframe:
12 months

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: Percent of Patients				
number (not applicable)	9.5	7.9		

Statistical analyses

Statistical analysis title	Incidence of BPAR, graft loss or death
Comparison groups	Everolimus/Tacrolimus v Tacrolimus
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.699
Method	Fisher exact

Secondary: Incidence of HCV

End point title	Incidence of HCV

End point description:
Incidence of HCV (hepatitis C virus) assessed as treatment emergent adverse events of special interest

End point type	Secondary

End point timeframe:
12 months

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: Participants	6	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of HCV related fibrosis

End point title	Incidence of HCV related fibrosis

End point description:

Incidence of hepatitis C virus (HCV) related fibrosis assessed as treatment emergent adverse events of special interest

End point type	Secondary

End point timeframe:

12 months

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of de novo HCC malignancies

End point title	Incidence of de novo HCC malignancies

End point description:

Incidence of de novo Hepatocellular Carcinoma (HCC) malignancies assessed as treatment emergent adverse events of special interest

End point type	Secondary

End point timeframe:

12 months

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: Participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and severity of CMV viral infections.

End point title	Incidence and severity of CMV viral infections.

End point description:

Incidence and severity of cytomegalovirus (CMV) viral infections assessed as treatment emergent adverse events of special interest.

End point type	Secondary

End point timeframe:

12 months

End point values	Everolimus/Tacrolimus	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	164		
Units: Participants				
No CMV viral infection	136	129		
Asymptomatic	0	5		
Mild	16	20		
Moderate	13	9		
Severe	4	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	EVR/TAC group
Reporting group description:	
EVR/TAC group	
Reporting group title	TAC group
Reporting group description:	
TAC group	

Serious adverse events	EVR/TAC group	TAC group	
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 169 (65.68%)	101 / 164 (61.59%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
CHRONIC MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOCELLULAR CARCINOMA			

subjects affected / exposed	0 / 169 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ANGIODYSPLASIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERY DISSECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DIABETIC VASCULAR DISORDER			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			

subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFERIOR VENA CAVA STENOSIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNAL HAEMORRHAGE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LYMPHATIC FISTULA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	2 / 169 (1.18%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POOR PERIPHERAL CIRCULATION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	2 / 169 (1.18%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	1 / 169 (0.59%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED HERNIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	4 / 169 (2.37%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SURGICAL FAILURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
LIVER TRANSPLANT REJECTION			
subjects affected / exposed	12 / 169 (7.10%)	9 / 164 (5.49%)	
occurrences causally related to treatment / all	4 / 14	1 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

DYSPNOEA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	4 / 169 (2.37%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
PLEURISY			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

DISORIENTATION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE OCCLUSION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			

subjects affected / exposed	3 / 169 (1.78%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 169 (0.00%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST X-RAY ABNORMAL			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 169 (1.78%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLUTAMATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOGLOBIN DECREASED			
subjects affected / exposed	2 / 169 (1.18%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ARTERY FLOW DECREASED			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			

subjects affected / exposed	6 / 169 (3.55%)	7 / 164 (4.27%)	
occurrences causally related to treatment / all	1 / 6	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	3 / 169 (1.78%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	2 / 169 (1.18%)	6 / 164 (3.66%)	
occurrences causally related to treatment / all	0 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
TROPONIN INCREASED			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ABDOMINAL WOUND DEHISCENCE			
subjects affected / exposed	3 / 169 (1.78%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACCIDENTAL OVERDOSE			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANASTOMOTIC STENOSIS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY ANASTOMOSIS			

COMPLICATION			
subjects affected / exposed	8 / 169 (4.73%)	13 / 164 (7.93%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN CONTUSION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLICATIONS OF TRANSPLANTED LIVER			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONCUSSION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GRAFT LOSS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED INCISIONAL HERNIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			

subjects affected / exposed	11 / 169 (6.51%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERDOSE			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL BILE LEAK			
subjects affected / exposed	1 / 169 (0.59%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC VERTEBRAL FRACTURE			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSPLANT FAILURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ULNA FRACTURE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEANING FAILURE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND DEHISCENCE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 169 (0.59%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LACUNAR STROKE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAPARESIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYNEUROPATHY			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TREMOR			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 169 (2.37%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE MARROW TOXICITY			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EVANS SYNDROME			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCHROMIC ANAEMIA			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTOSIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	3 / 169 (1.78%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
MYDRIASIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	3 / 169 (1.78%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ABDOMINAL PAIN			
subjects affected / exposed	2 / 169 (1.18%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHTHOUS ULCER			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	5 / 169 (2.96%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	1 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DENTAL CARIES			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	5 / 169 (2.96%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	1 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAECES DISCOLOURED			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
GASTRITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL ANGIODYSPLASIA HAEMORRHAGIC			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFLAMMATION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL NECROSIS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED GASTRIC EMPTYING			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED INGUINAL HERNIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED UMBILICAL HERNIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL INFARCTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL ISCHAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRA-ABDOMINAL FLUID COLLECTION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MESENTERIC VEIN THROMBOSIS			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MESENTERIC VENOUS OCCLUSION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	3 / 169 (1.78%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	2 / 169 (1.18%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBILEUS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SWOLLEN TONGUE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UMBILICAL HERNIA			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			

subjects affected / exposed	4 / 169 (2.37%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
ACUTE HEPATIC FAILURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
BILE DUCT STENOSIS			
subjects affected / exposed	5 / 169 (2.96%)	6 / 164 (3.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILE DUCT STONE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY ISCHAEMIA			
subjects affected / exposed	5 / 169 (2.96%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY TRACT DISORDER			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
BILOMA			
subjects affected / exposed	2 / 169 (1.18%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS			
subjects affected / exposed	13 / 169 (7.69%)	7 / 164 (4.27%)	
occurrences causally related to treatment / all	1 / 22	2 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
CHOLANGITIS ACUTE			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			
subjects affected / exposed	1 / 169 (0.59%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ARTERY ANEURYSM			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEPATIC ARTERY STENOSIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ARTERY THROMBOSIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEPATIC FAILURE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC HAEMATOMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC HAEMORRHAGE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC INFARCTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ISCHAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEPATIC LESION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC NECROSIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC STEATOSIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS TOXIC			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER DISORDER			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-ALCOHOLIC STEATOHEPATITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PORTAL VEIN THROMBOSIS			
subjects affected / exposed	0 / 169 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VANISHING BILE DUCT SYNDROME			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRURITUS			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	10 / 169 (5.92%)	8 / 164 (4.88%)	
occurrences causally related to treatment / all	5 / 12	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
ALBUMINURIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS HAEMORRHAGIC			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IGA NEPHROPATHY			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OLIGURIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRERENAL FAILURE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROTEINURIA			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			

subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
GOITRE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC NODULAR GOITRE			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL DISORDER			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOPATHY			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL WALL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS JAW			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
BACTERIAL INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY ABSCESS			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
BILIARY TRACT INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS INFECTIVE			
subjects affected / exposed	6 / 169 (3.55%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 23	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS COLITIS			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS HEPATITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			

subjects affected / exposed	6 / 169 (3.55%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	3 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS SYNDROME			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS VIRAEMIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMPYEMA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS INFECTIOUS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPIDIDYMITIS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPSTEIN-BARR VIRUS INFECTION			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOLLICULITIS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FUNGAL INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	3 / 169 (1.78%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS CLOSTRIDIAL			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS CRYPTOSPORIDIAL			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS ROTAVIRUS			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL VIRAL INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA INFECTION			
subjects affected / exposed	2 / 169 (1.18%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS C			
subjects affected / exposed	2 / 169 (1.18%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 169 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMAN HERPESVIRUS 6 INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SEROMA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			

subjects affected / exposed	4 / 169 (2.37%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	2 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER ABSCESS			
subjects affected / exposed	5 / 169 (2.96%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
LOCALISED INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARONYCHIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS BACTERIAL			
subjects affected / exposed	2 / 169 (1.18%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGEAL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PILONIDAL CYST			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	10 / 169 (5.92%)	7 / 164 (4.27%)	
occurrences causally related to treatment / all	5 / 15	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
PSEUDOMONAS INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCARLET FEVER			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 169 (1.18%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	2 / 169 (1.18%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSPLANT ABSCESS			

subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 169 (1.18%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
VARICELLA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 169 (1.18%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	3 / 169 (1.78%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION STAPHYLOCOCCAL			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ACIDOSIS HYPERCHLORAEMIC			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			

subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC COMPLICATION			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID RETENTION			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 169 (1.78%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERINSULINAEMIC HYPOGLYCAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	3 / 169 (1.78%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (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	EVR/TAC group	TAC group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 169 (97.04%)	153 / 164 (93.29%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	28 / 169 (16.57%)	24 / 164 (14.63%)	
occurrences (all)	28	24	
General disorders and administration site conditions			
IMPAIRED HEALING			
subjects affected / exposed	24 / 169 (14.20%)	10 / 164 (6.10%)	
occurrences (all)	24	10	
OEDEMA PERIPHERAL			
subjects affected / exposed	38 / 169 (22.49%)	15 / 164 (9.15%)	
occurrences (all)	44	16	
PYREXIA			
subjects affected / exposed	20 / 169 (11.83%)	9 / 164 (5.49%)	
occurrences (all)	29	10	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	14 / 169 (8.28%)	8 / 164 (4.88%)	
occurrences (all)	15	9	
DYSPNOEA			
subjects affected / exposed	9 / 169 (5.33%)	7 / 164 (4.27%)	
occurrences (all)	10	7	
PLEURAL EFFUSION			
subjects affected / exposed	20 / 169 (11.83%)	12 / 164 (7.32%)	
occurrences (all)	27	12	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	4 / 169 (2.37%)	10 / 164 (6.10%)	
occurrences (all)	4	10	
INSOMNIA			
subjects affected / exposed	1 / 169 (0.59%)	9 / 164 (5.49%)	
occurrences (all)	1	10	

Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	21 / 169 (12.43%)	21 / 164 (12.80%)	
occurrences (all)	21	24	
BODY TEMPERATURE INCREASED			
subjects affected / exposed	6 / 169 (3.55%)	9 / 164 (5.49%)	
occurrences (all)	8	12	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	18 / 169 (10.65%)	9 / 164 (5.49%)	
occurrences (all)	18	9	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	10 / 169 (5.92%)	12 / 164 (7.32%)	
occurrences (all)	10	14	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	9 / 169 (5.33%)	13 / 164 (7.93%)	
occurrences (all)	11	13	
TRANSAMINASES INCREASED			
subjects affected / exposed	9 / 169 (5.33%)	8 / 164 (4.88%)	
occurrences (all)	9	9	
Injury, poisoning and procedural complications			
INCISIONAL HERNIA			
subjects affected / exposed	35 / 169 (20.71%)	10 / 164 (6.10%)	
occurrences (all)	35	10	
PROCEDURAL PAIN			
subjects affected / exposed	5 / 169 (2.96%)	9 / 164 (5.49%)	
occurrences (all)	5	10	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	48 / 169 (28.40%)	22 / 164 (13.41%)	
occurrences (all)	60	27	
TREMOR			
subjects affected / exposed	25 / 169 (14.79%)	23 / 164 (14.02%)	
occurrences (all)	25	23	
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	22 / 169 (13.02%)	20 / 164 (12.20%)	
occurrences (all)	24	21	
LEUKOPENIA			
subjects affected / exposed	45 / 169 (26.63%)	12 / 164 (7.32%)	
occurrences (all)	49	13	
THROMBOCYTOPENIA			
subjects affected / exposed	25 / 169 (14.79%)	4 / 164 (2.44%)	
occurrences (all)	27	5	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	23 / 169 (13.61%)	17 / 164 (10.37%)	
occurrences (all)	26	19	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	15 / 169 (8.88%)	11 / 164 (6.71%)	
occurrences (all)	16	13	
APHTHOUS ULCER			
subjects affected / exposed	11 / 169 (6.51%)	0 / 164 (0.00%)	
occurrences (all)	11	0	
ASCITES			
subjects affected / exposed	20 / 169 (11.83%)	13 / 164 (7.93%)	
occurrences (all)	20	15	
CONSTIPATION			
subjects affected / exposed	13 / 169 (7.69%)	10 / 164 (6.10%)	
occurrences (all)	13	10	
DIARRHOEA			
subjects affected / exposed	43 / 169 (25.44%)	39 / 164 (23.78%)	
occurrences (all)	60	41	
NAUSEA			
subjects affected / exposed	22 / 169 (13.02%)	13 / 164 (7.93%)	
occurrences (all)	26	15	
VOMITING			
subjects affected / exposed	16 / 169 (9.47%)	12 / 164 (7.32%)	
occurrences (all)	23	17	
Hepatobiliary disorders			
CHOLANGITIS			

subjects affected / exposed	9 / 169 (5.33%)	2 / 164 (1.22%)	
occurrences (all)	11	2	
HEPATIC CYST			
subjects affected / exposed	10 / 169 (5.92%)	3 / 164 (1.83%)	
occurrences (all)	14	3	
HEPATIC STEATOSIS			
subjects affected / exposed	12 / 169 (7.10%)	8 / 164 (4.88%)	
occurrences (all)	13	8	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	10 / 169 (5.92%)	5 / 164 (3.05%)	
occurrences (all)	10	5	
PRURITUS			
subjects affected / exposed	16 / 169 (9.47%)	10 / 164 (6.10%)	
occurrences (all)	16	13	
Renal and urinary disorders			
PROTEINURIA			
subjects affected / exposed	26 / 169 (15.38%)	12 / 164 (7.32%)	
occurrences (all)	29	13	
RENAL FAILURE			
subjects affected / exposed	12 / 169 (7.10%)	15 / 164 (9.15%)	
occurrences (all)	13	16	
RENAL IMPAIRMENT			
subjects affected / exposed	7 / 169 (4.14%)	15 / 164 (9.15%)	
occurrences (all)	7	15	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	9 / 169 (5.33%)	8 / 164 (4.88%)	
occurrences (all)	9	9	
BACK PAIN			
subjects affected / exposed	17 / 169 (10.06%)	12 / 164 (7.32%)	
occurrences (all)	17	12	
MUSCLE SPASMS			
subjects affected / exposed	7 / 169 (4.14%)	9 / 164 (5.49%)	
occurrences (all)	7	9	
PAIN IN EXTREMITY			

subjects affected / exposed	11 / 169 (6.51%)	5 / 164 (3.05%)	
occurrences (all)	12	5	
Infections and infestations			
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	24 / 169 (14.20%)	28 / 164 (17.07%)	
occurrences (all)	33	34	
URINARY TRACT INFECTION			
subjects affected / exposed	30 / 169 (17.75%)	24 / 164 (14.63%)	
occurrences (all)	41	36	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	41 / 169 (24.26%)	29 / 164 (17.68%)	
occurrences (all)	53	36	
Metabolism and nutrition disorders			
DIABETES MELLITUS			
subjects affected / exposed	11 / 169 (6.51%)	8 / 164 (4.88%)	
occurrences (all)	11	8	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	30 / 169 (17.75%)	9 / 164 (5.49%)	
occurrences (all)	32	9	
HYPERKALAEMIA			
subjects affected / exposed	13 / 169 (7.69%)	17 / 164 (10.37%)	
occurrences (all)	14	18	
HYPERLIPIDAEMIA			
subjects affected / exposed	15 / 169 (8.88%)	2 / 164 (1.22%)	
occurrences (all)	15	2	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	18 / 169 (10.65%)	8 / 164 (4.88%)	
occurrences (all)	19	8	
HYPERURICAEMIA			
subjects affected / exposed	10 / 169 (5.92%)	8 / 164 (4.88%)	
occurrences (all)	10	8	
HYPOKALAEMIA			
subjects affected / exposed	11 / 169 (6.51%)	8 / 164 (4.88%)	
occurrences (all)	15	9	
IRON DEFICIENCY			

subjects affected / exposed	11 / 169 (6.51%)	5 / 164 (3.05%)	
occurrences (all)	11	5	
VITAMIN D DEFICIENCY			
subjects affected / exposed	11 / 169 (6.51%)	10 / 164 (6.10%)	
occurrences (all)	11	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2012	Assessment schedule: Laboratory and GFR were shifted from Screening visit to baseline visit. Additional assessment in Screening visit: Menopausal status and a pregnancy test in all women of childbearing potential.
26 September 2012	To allow more patients to be randomized into this study in- and exclusion criteria were adapted. According to these adaptations the patient management was changed. In addition some editorial changes and changes regarding the statistical analysis were performed.
14 June 2013	Details of five sub-studies which were conducted in selected centers were added
19 November 2014	The protocol has been refined to clarify the mandatory usage of corticosteroids in this study. Additionally, Inclusion Criterion 3/Exclusion Criterion 11 has been adjusted to include total abstinence as acceptable contraception method. In addition some editorial changes were performed.
19 August 2015	Exclusion Criterion 5 (at randomization) has been adjusted to allow inclusion of patients with hemoglobin < 6.0 g/dL (transfusion of erythrocytes concentrate during or after transplantation are allowed according to investigator discretion.)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported