Clinical trial results:
A 24 month, randomized, controlled, study to evaluate the efficacy and safety of concentration-controlled everolimus plus reduced tacrolimus compared to standard tacrolimus in recipients of living donor liver transplants and long term extension to evaluate the efficacy and safety of concentration-controlled everolimus plus reduced tacrolimus compared to standard tacrolimus in recipients of living donor liver transplants in Japan

Summary

EudraCT number	2010-024527-25
Trial protocol	IT DE
Global end of trial date	10 October 2017

Results information

Result version number	v2 (current)
This version publication date	16 March 2019
First version publication date	21 October 2018
Version creation reason	• New data added to full data set To add data for the extension trial (CRAD001H2307E1).

Trial information

Trial identification

Sponsor protocol code	CRAD001H2307 and CRAD001H2307E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01888432
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	10 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate comparable efficacy as measured by the composite efficacy failure of tBPAR, GL or death (D) with everolimus in combination with reduced tacrolimus compared to standard exposure tacrolimus, at 12 months post-transplantation, in living donor 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: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2013
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	India: 29
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Taiwan: 79
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Egypt: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Japan: 28
Worldwide total number of subjects	284
EEA total number of subjects	7

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)	284
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In all, 284 patients were randomized after transplantation to EVR+Reduced TAC group and TAC Control group. Two patients were not eligible and randomized in IRT by mistake and to whom no study medication was given, and so did not have their data included

Pre-assignment

Screening details:

A total of 494 patients were screened. Of these, 448 patients received a liver transplant and entered the run-in period.

Data reported here are the CRAD001H2307 core study results and its extension (CRAD001H2307E1).

Period 1

Period 1 title	12-month analysis (FAS)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	EVR+Reduced TAC

Arm description:

Everolimus + reduced tacrolimus ± corticosteroids

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

Dosage and administration details:

as 1.0 mg, 0.75 and 0.50 mg tablets

Arm title	TAC Control

Arm description:

Standard tacrolimus ± corticosteroids

Arm type	Active comparator
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, 1.0 mg and 5.0 mg capsules

Number of subjects in period 1	EVR+Reduced TAC	TAC Control
Started	142	142
Completed	131	133
Not completed	11	9
Adverse event, serious fatal	4	3
Physician decision	1	1
Consent withdrawn by subject	6	3
Lost to follow-up	-	2

Period 2	
Period 2 title	24-month analysis (FAS)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	EVR+Reduced TAC

Arm description:

Everolimus + reduced tacrolimus ± corticosteroids

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

Dosage and administration details:

as 1.0 mg, 0.75 and 0.50 mg tablets

Arm title	TAC Control

Arm description:

Standard tacrolimus ± corticosteroids

Arm type	Active comparator
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, 1.0 mg and 5.0 mg capsules

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The study has an long term extension (CRAD001H2307E1) in Japan and approximately 28 patients were to be included to evaluate the long-term efficacy and safety of concentration controlled everolimus regimen plus reduced tacrolimus compared to standard tacrolimus in recipients of living donor liver transplants in Japan who participated in the CRAD001H2307 study.

Data reported in this period are from the extension trial (CRAD001H2307E1).

Number of subjects in period 2	EVR+Reduced TAC	TAC Control
Started	142	142
Completed	125	125
Not completed	17	17
Adverse event, serious fatal	8	4
Physician decision	2	4
Consent withdrawn by subject	7	6
Graft loss	-	1
Lost to follow-up	-	2

Period 3	
Period 3 title	36-month analysis (extension)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	EVR+Reduced TAC
Arm description: Everolimus + reduced tacrolimus ± corticosteroids	
Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Intravenous use, Oral use
Dosage and administration details: as 1.0 mg, 0.75 and 0.50 mg tablets	
Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 0.5 mg, 1.0 mg and 5.0 mg capsules	
Arm title	TAC Control
Arm description: Standard tacrolimus ± corticosteroids	
Arm type	Active comparator

Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, 1.0 mg and 5.0 mg capsules

Number of subjects in period 3[2]	EVR+Reduced TAC	TAC Control
Started	13	5
Completed	12	5
Not completed	1	0
Adverse event, serious fatal	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The study has an long term extension (CRAD001H2307E1) in Japan and approximately 28 patients were to be included to evaluate the long-term efficacy and safety of concentration controlled everolimus regimen plus reduced tacrolimus compared to standard tacrolimus in recipients of living donor liver transplants in Japan who participated in the CRAD001H2307 study.
Data reported in this period are from the extension trial (CRAD001H2307E1).

Baseline characteristics

Reporting groups	
Reporting group title	EVR+Reduced TAC
Reporting group description:	
Everolimus + reduced tacrolimus ± corticosteroids	
Reporting group title	TAC Control
Reporting group description:	
Standard tacrolimus ± corticosteroids	

Reporting group values	EVR+Reduced TAC	TAC Control	Total
Number of subjects	142	142	284
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)	142	142	284
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	54.2	52.7	
standard deviation	± 8.95	± 10.41	-
Sex: Female, Male Units: Subjects			
Female	38	43	81
Male	104	99	203
Race/Ethnicity, Customized Units: Subjects			
Caucasian	30	30	60
Asian	111	112	223
Other	1	0	1

End points

End points reporting groups	
Reporting group title	EVR+Reduced TAC
Reporting group description: Everolimus + reduced tacrolimus ± corticosteroids	
Reporting group title	TAC Control
Reporting group description: Standard tacrolimus ± corticosteroids	
Reporting group title	EVR+Reduced TAC
Reporting group description: Everolimus + reduced tacrolimus ± corticosteroids	
Reporting group title	TAC Control
Reporting group description: Standard tacrolimus ± corticosteroids	
Reporting group title	EVR+Reduced TAC
Reporting group description: Everolimus + reduced tacrolimus ± corticosteroids	
Reporting group title	TAC Control
Reporting group description: Standard tacrolimus ± corticosteroids	

Primary: Number of participants with composite efficacy failure of treated biopsy proven acute rejection, graft loss or death in everolimus with reduced tacrolimus group compared to standard tacrolimus	
End point title	Number of participants with composite efficacy failure of treated biopsy proven acute rejection, graft loss or death in everolimus with reduced tacrolimus group compared to standard tacrolimus
End point description: Rate of composite efficacy failure of treated biopsy proven acute rejection (tBPAR ≥ RAI score 3), graft loss (GL) or death (D) in everolimus with reduced tacrolimus group compared to standard tacrolimus at 12 months	
End point type	Primary
End point timeframe: 12 months post transplantation	

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants	7	8		

Statistical analyses

Statistical analysis title	12-month analysis (FAS)

Statistical analysis description:

non-inferior efficacy failure of the reduced tacrolimus regimen to control by rejecting the null hypothesis.

Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [1]
Method	Z-test
Parameter estimate	Kaplan-Meier
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.2
upper limit	3.7

Notes:

[1] - Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is for one-sided test and should
be compared to 0.05 significance level.

Secondary: Renal function by estimated glomerular filtration rate (eGFR) from randomization

End point title	Renal function by estimated glomerular filtration rate (eGFR) from randomization

End point description:

Renal function (change in estimated glomerular filtration rate (eGFR)) from randomization to Month 12 post transplantation with everolimus (EVR) in combination with reduced tacrolimus (rTAC) compared to standard exposure tacrolimus (TAC) in living donor liver transplant recipients.

End point type	Secondary

End point timeframe:

Month 12

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: mL/min/1.73 m^2				
least squares mean (standard error)	-7.94 (± 1.839)	-12.09 (± 1.824)		

Statistical analyses

Statistical analysis title	12-month
Comparison groups	EVR+Reduced TAC v TAC Control

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	4.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.09
upper limit	8.4
Variability estimate	Standard error of the mean
Dispersion value	2.574

Secondary: Compare renal function over time assessed by the change by eGFR, post-randomization

End point title	Compare renal function over time assessed by the change by eGFR, post-randomization

End point description:

Compare evolution of post-randomization renal function over time assessed by the change in estimated GFR (MDRD-4), including changes from randomization to Months 12 and 24. Rate of change of renal function.

End point type	Secondary

End point timeframe:

Month 24

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Paricipants				
least squares mean (standard error)	-11.01 (± 1.928)	-14.26 (± 1.914)		

Statistical analyses

Statistical analysis title	12-month
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.25

Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.21
upper limit	7.7
Variability estimate	Standard error of the mean
Dispersion value	2.699

Secondary: Compare incidence of a composite of tBPAR, graft loss, and death

End point title	Compare incidence of a composite of tBPAR, graft loss, and death

End point description:

Compare between the treatment group EVR with rTAC vs standard TAC: incidence of a composite of tBPAR, graft loss, death

End point type	Secondary

End point timeframe:

Month 24 post transplantation

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participant				
tBPAR/graft loss/death|	12	11		
On-treatment tBPAR/graft loss/death|	7	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Compare incidence of tBPAR

End point title	Compare incidence of tBPAR

End point description:

Compare between the treatment group EVR with rTAC vs standard TAC: Incidence of tBPAR

End point type	Secondary

End point timeframe:

Month 12 and Month 24 post transplantation

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
tBPAR - month 12|	3	5		
tBPAR - month 24|	4	6		
On-treatment tBPAR - month 24|	3	6		

Statistical analyses

Statistical analysis title	Month 12
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	-1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.7
upper limit	2

Statistical analysis title	Month 24 (tBPAR)
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	-1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.1
upper limit	2.6

Statistical analysis title	Month 24 (on-treatment tBPAR)
Comparison groups	EVR+Reduced TAC v TAC Control

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	-2.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.7
upper limit	1.4

Secondary: Compare incidence of BPAR

End point title	Compare incidence of BPAR

End point description:

Compare between the treatment group EVR with rTAC vs standard TAC: incidence of a composite of biopsy proven acute rejection (BPAR)

End point type	Secondary

End point timeframe:

Month 12 and Month 24 post transplantation

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	7	6		
Month 24|	8	7		

Statistical analyses

Statistical analysis title	Month 12
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.4
upper limit	5.1

Statistical analysis title	Month 24
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.6
upper limit	5.6

Secondary: Compare incidence of graft loss	
End point title	Compare incidence of graft loss
End point description: Compare between the treatment group EVR with rTAC vs standard TAC: incidence of graft loss	
End point type	Secondary
End point timeframe: Month 12 and Month 24 post transplantation	

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	0	0		
month 24|	0	1		
month 24 (on-treatment graft loss)|	0	0		

Statistical analyses

Statistical analysis title	graft loss at month 24
Comparison groups	EVR+Reduced TAC v TAC Control

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	-0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.1
upper limit	0.5

Secondary: Compare incidence of a composite of death or graft loss	
End point title	Compare incidence of a composite of death or graft loss
End point description:	
Compare between the treatment group EVR with rTAC vs standard TAC: Incidence of a composite of death or graft loss	
End point type	Secondary
End point timeframe:	
Month 12 and Month 24 post transplantation	

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	4	3		
Month 24|	8	5		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	2.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.1
upper limit	6.6

Statistical analysis title	Month 12
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.5
upper limit	3.8

Secondary: Compare incidence of death	
End point title	Compare incidence of death
End point description: Compare between the treatment group EVR with rTAC vs standard TAC: incidence of death	
End point type	Secondary
End point timeframe: Month 12 and Month 24 post transplantation	

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	4	3		
Month 24|	8	4		
Month 24 (on-treatment death)|	4	3		

Statistical analyses

Statistical analysis title	Month 12
Comparison groups	EVR+Reduced TAC v TAC Control

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.5
upper limit	3.8

Statistical analysis title	Month 24
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.1
upper limit	7.2

Statistical analysis title	Month 24 (On-treatment death)
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Kaplan-Meier
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.5
upper limit	3.9

Secondary: Compare incidence of AR	
End point title	Compare incidence of AR
End point description:	
Compare between the treatment group EVR with rTAC vs standard TAC: incidence of acute rejection (AR)	
End point type	Secondary

End point timeframe:
Month 12 and Month 24 post transplantation

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	9	8		
Month 24|	12	9		

Statistical analyses

Statistical analysis title	Incidence rate of AR - month 12
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.9
upper limit	5.3

Statistical analysis title	Incidence rate of AR - month 24
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	2.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3
upper limit	7.2

Secondary: Compare incidence of tAR

End point title	Compare incidence of tAR

End point description:

Compare between the treatment group EVR with rTAC vs standard TAC: incidence of treated acute rejection (tAR).

End point type	Secondary

End point timeframe:

Month 12 and Month 24 post transplantation

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	142		
Units: Participants				
Month 12|	5	6		
Month 24|	7	7		

Statistical analyses

Statistical analysis title	Incidence rate of tAR - month 12
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.5
upper limit	3.1

Statistical analysis title	Incidence rate of tAR - month 24
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.2
upper limit	4.2

Secondary: Compare time to recurrence of HCC in subjects with a diagnosis of HCC at the time of liver transplantation

End point title	Compare time to recurrence of HCC in subjects with a diagnosis of HCC at the time of liver transplantation

End point description:

Patients transplanted for HCC or with HCC diagnosed at time of transplantation were monitored for HCC recurrence according to local practice. For example routine laboratory monitoring/tests, tumor markers, hepatic ultrasound, computed tomography scans (CAT, CT) or MRI (especially Fe-MRI) on a regular basis per local practice.

End point type	Secondary

End point timeframe:

Month 12 and Month 24

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	141		
Units: Participants				
HCC recurrence (n/M) - month 12|	0	5		
HCC recurrence (n/M) - month 24|	1	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects experiencing adverse events/infections by SOC

End point title	Number of subjects experiencing adverse events/infections by SOC

End point description:

End point type	Secondary

End point timeframe:

Month 24

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	141		
Units: Participants				
Any AE/infection|	140	136		
Blood and lymphatic system disorders|	44	32		
Cardiac disorders|	15	12		

Congenital, familial and genetic disorders|	1	2		
Ear and labyrinth disorders|	2	5		
Endocrine disorders|	1	2		
Eye disorders|	17	15		
Gastrointestinal disorders|	98	74		
General disorders&admin site conditions|	48	42		
Hepatobiliary disorders|	44	40		
Immune system disorders|	8	11		
Infections and infestations|	84	70		
Injury, poisoning&proced. complications|	36	28		
Investigations|	61	68		
Metabolism and nutrition disorders|	87	60		
Musculoskeletal and connective tissue disorders|	30	43		
Neo benign, malig&unspecified (cysts&polyps)|	10	17		
Nervous system disorders|	38	44		
Product issues#|	1	1		
Psychiatric disorders|	33	26		
Renal and urinary disorders|	46	36		
Reproductive system&breast dis.|	9	12		
Respiratory, thoracic&mediastinal dis.|	34	39		
Skin&subcutaneous tissue disorders|	39	44		
Vascular disorders|	38	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Compare incidence of notable safety events (SAEs, infections and serious infections leading to premature discontinuation)

End point title	Compare incidence of notable safety events (SAEs, infections and serious infections leading to premature discontinuation)

End point description:

Notable events include death, Serious AE/infection,, and AE/infection leading to discontinuation of study medication.

End point type	Secondary

End point timeframe:

Month 24

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	141		
Units: Participants				
Any notable events|	86	82		
Death|	8	4		
Serious AE/Infection|	83	78		
AE/Infection lead. to premature disc of study med|	21	18		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Composite efficacy failure of treated biopsy in everolimus with reduced tacrolimus group compared to standard tacrolimus in patients from Japan only

End point title	Composite efficacy failure of treated biopsy in everolimus with reduced tacrolimus group compared to standard tacrolimus in patients from Japan only

End point description:

Rate of composite efficacy failure of treated biopsy in everolimus with reduced tacrolimus group compared to standard tacrolimus from randomization in core study up to 36 months in the extension study.
Composite endpoint = treated BPAR, graft loss or death. AR = Acute rejection; tAR = treated AR; BPR = biopsy proven rejection; BPAR = biopsy proven acute rejection; tBPAR = treated BPAR

End point type	Other pre-specified

End point timeframe:

From randomization in core study up to 36 months post transplantion

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Participants				
Composite endpoint	2	1		
On-treatment composite endpoint	1	0		
Graft loss/death	1	1		
tBPAR	2	0		
Graft loss	0	1		
Death	1	0		
AR	3	2		
tAR	2	0		
BPR	6	3		
BPAR	3	2		

Statistical analyses

Statistical analysis title	Composite endpoint up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.9
upper limit	30.6

Statistical analysis title	On-treatment composite endpoint up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	19.3

Statistical analysis title	Graft loss/death at up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.6
upper limit	28.7

Statistical analysis title	tBPAR up to 36 months
Comparison groups	TAC Control v EVR+Reduced TAC

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	33.1

Statistical analysis title	Death up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	31.6

Statistical analysis title	AR up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.9
upper limit	35.2

Statistical analysis title	tAR up to 36 months
Comparison groups	TAC Control v EVR+Reduced TAC

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	33.1

Statistical analysis title	BPR up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	52.1

Statistical analysis title	BPAR up to 36 months
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Kaplan-Meier estimate
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.9
upper limit	35.2

Other pre-specified: Renal function by estimated Glomerular Filtration Rate (all extension patients)

End point title	Renal function by estimated Glomerular Filtration Rate (all extension patients)

End point description:

Renal function (change in estimated glomerular filtration rate (eGFR)) from randomization to Month 36 post transplantation with everolimus (EVR) in combination with reduced tacrolimus (rTAC) compared to standard exposure tacrolimus (TAC) in living donor liver transplant recipients in Japan.

End point type	Other pre-specified
End point timeframe: randomization, at 36 months post transplantation	

End point values	EVR+Reduced TAC	TAC Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	5		
Units: mL/min/1.73m2				
least squares mean (standard error)	-26.88 (± 10.114)	-16.87 (± 19.412)		

Statistical analyses

Statistical analysis title	eGFR (all extension patients)
Comparison groups	EVR+Reduced TAC v TAC Control
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	-10.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.91
upper limit	39.89
Variability estimate	Standard error of the mean
Dispersion value	22.059

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 4 years.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	EVR+Reduced TAC
Reporting group description: EVR+Reduced TAC	
Reporting group title	TAC Control
Reporting group description: TAC Control	

Serious adverse events	EVR+Reduced TAC	TAC Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 142 (58.45%)	78 / 141 (55.32%)	
number of deaths (all causes)	8	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone giant cell tumour			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic angiosarcoma			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 142 (0.70%)	4 / 141 (2.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lipofibroma			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 142 (0.00%)	5 / 141 (3.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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 the hypopharynx			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hot flush			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiopathy			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crepitations			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 142 (7.75%)	8 / 141 (5.67%)	
occurrences causally related to treatment / all	2 / 15	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Liver transplant rejection			
subjects affected / exposed	3 / 142 (2.11%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	2 / 142 (1.41%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal ulceration			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
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 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary mass			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wheezing			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	4 / 142 (2.82%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 7	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level increased			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 142 (0.70%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			

subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary anastomosis complication			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical peritonitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site pain			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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	5 / 142 (3.52%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural bile leak			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 142 (1.41%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac discomfort			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tremor			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's encephalopathy			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 142 (1.41%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lens dislocation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	3 / 142 (2.11%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	7 / 142 (4.93%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal incontinence			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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 / 142 (0.00%)	1 / 141 (0.71%)	
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	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoplakia oral			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric haemorrhage			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pouchitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestine ulcer			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	10 / 142 (7.04%)	6 / 141 (4.26%)	
occurrences causally related to treatment / all	0 / 19	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary cirrhosis primary			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			

subjects affected / exposed	1 / 142 (0.70%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	8 / 142 (5.63%)	9 / 141 (6.38%)	
occurrences causally related to treatment / all	2 / 12	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis obstructive			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation intrahepatic duct acquired			
subjects affected / exposed	1 / 142 (0.70%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery thrombosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein stenosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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			
Skin ulcer			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 142 (1.41%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chromaturia			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			

subjects affected / exposed	1 / 142 (0.70%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 142 (2.11%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 142 (2.11%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 142 (2.82%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	5 / 142 (3.52%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	2 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis E			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Orchitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 142 (7.04%)	5 / 141 (3.55%)	
occurrences causally related to treatment / all	2 / 11	1 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 142 (0.70%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 142 (2.11%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 142 (0.70%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 142 (0.70%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 142 (1.41%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EVR+Reduced TAC	TAC Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 142 (88.03%)	120 / 141 (85.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 142 (20.42%)	23 / 141 (16.31%)	
occurrences (all)	31	25	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	16 / 142 (11.27%)	8 / 141 (5.67%)	
occurrences (all)	17	11	
Pyrexia			
subjects affected / exposed	18 / 142 (12.68%)	20 / 141 (14.18%)	
occurrences (all)	40	29	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 142 (8.45%)	15 / 141 (10.64%)	
occurrences (all)	14	16	
Psychiatric disorders			
Depression			

subjects affected / exposed	2 / 142 (1.41%)	8 / 141 (5.67%)	
occurrences (all)	2	8	
Insomnia			
subjects affected / exposed	26 / 142 (18.31%)	13 / 141 (9.22%)	
occurrences (all)	31	17	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 142 (3.52%)	8 / 141 (5.67%)	
occurrences (all)	5	8	
Blood creatinine increased			
subjects affected / exposed	10 / 142 (7.04%)	13 / 141 (9.22%)	
occurrences (all)	11	21	
Hepatic enzyme abnormal			
subjects affected / exposed	8 / 142 (5.63%)	19 / 141 (13.48%)	
occurrences (all)	13	36	
Hepatic enzyme increased			
subjects affected / exposed	16 / 142 (11.27%)	19 / 141 (13.48%)	
occurrences (all)	21	29	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 142 (2.11%)	9 / 141 (6.38%)	
occurrences (all)	3	9	
Headache			
subjects affected / exposed	19 / 142 (13.38%)	14 / 141 (9.93%)	
occurrences (all)	21	18	
Tremor			
subjects affected / exposed	4 / 142 (2.82%)	11 / 141 (7.80%)	
occurrences (all)	4	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 142 (12.68%)	15 / 141 (10.64%)	
occurrences (all)	20	20	
Leukopenia			
subjects affected / exposed	16 / 142 (11.27%)	7 / 141 (4.96%)	
occurrences (all)	34	8	
Thrombocytopenia			

subjects affected / exposed	14 / 142 (9.86%)	3 / 141 (2.13%)	
occurrences (all)	14	4	
Eye disorders			
Cataract			
subjects affected / exposed	8 / 142 (5.63%)	4 / 141 (2.84%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 142 (13.38%)	12 / 141 (8.51%)	
occurrences (all)	19	15	
Constipation			
subjects affected / exposed	13 / 142 (9.15%)	16 / 141 (11.35%)	
occurrences (all)	18	16	
Diarrhoea			
subjects affected / exposed	32 / 142 (22.54%)	19 / 141 (13.48%)	
occurrences (all)	41	28	
Nausea			
subjects affected / exposed	7 / 142 (4.93%)	9 / 141 (6.38%)	
occurrences (all)	7	9	
Mouth ulceration			
subjects affected / exposed	17 / 142 (11.97%)	6 / 141 (4.26%)	
occurrences (all)	18	7	
Stomatitis			
subjects affected / exposed	19 / 142 (13.38%)	5 / 141 (3.55%)	
occurrences (all)	25	6	
Vomiting			
subjects affected / exposed	7 / 142 (4.93%)	10 / 141 (7.09%)	
occurrences (all)	12	11	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	10 / 142 (7.04%)	7 / 141 (4.96%)	
occurrences (all)	10	7	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	22 / 142 (15.49%)	18 / 141 (12.77%)	
occurrences (all)	26	22	
Rash			

subjects affected / exposed	7 / 142 (4.93%)	10 / 141 (7.09%)	
occurrences (all)	11	10	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 142 (2.11%)	13 / 141 (9.22%)	
occurrences (all)	3	15	
Renal impairment			
subjects affected / exposed	11 / 142 (7.75%)	5 / 141 (3.55%)	
occurrences (all)	12	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 142 (3.52%)	9 / 141 (6.38%)	
occurrences (all)	5	9	
Back pain			
subjects affected / exposed	8 / 142 (5.63%)	10 / 141 (7.09%)	
occurrences (all)	8	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	20 / 142 (14.08%)	16 / 141 (11.35%)	
occurrences (all)	38	22	
Upper respiratory tract infection			
subjects affected / exposed	18 / 142 (12.68%)	11 / 141 (7.80%)	
occurrences (all)	25	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 142 (6.34%)	13 / 141 (9.22%)	
occurrences (all)	10	14	
Dyslipidaemia			
subjects affected / exposed	13 / 142 (9.15%)	4 / 141 (2.84%)	
occurrences (all)	14	5	
Hypercholesterolaemia			
subjects affected / exposed	22 / 142 (15.49%)	2 / 141 (1.42%)	
occurrences (all)	31	2	
Hyperkalaemia			
subjects affected / exposed	20 / 142 (14.08%)	13 / 141 (9.22%)	
occurrences (all)	25	21	

Hyperlipidaemia			
subjects affected / exposed	22 / 142 (15.49%)	8 / 141 (5.67%)	
occurrences (all)	23	8	
Hyperuricaemia			
subjects affected / exposed	7 / 142 (4.93%)	8 / 141 (5.67%)	
occurrences (all)	9	11	
Hypokalaemia			
subjects affected / exposed	10 / 142 (7.04%)	3 / 141 (2.13%)	
occurrences (all)	11	4	
Hypomagnesaemia			
subjects affected / exposed	10 / 142 (7.04%)	11 / 141 (7.80%)	
occurrences (all)	13	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	The amendment introduced the following changes: 1. The sample size reduction and power recalculation 2. A standardized definition for the assessment of NODM 3. The central reading of the tumor biopsy from the explanted liver of patients with HCC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data recorded here are the CRAD001H2307 core study results and its extension trial (CRAD001H2307E1) in Japan.

Notes: