



Clinical trial results:

A multicentre, randomised, open-label, controlled, 12-month follow-up study to assess impact on renal function of an immunosuppression regimen based on tacrolimus minimisation in association with everolimus in de novo liver transplant recipients. The REDUCE study.

Summary

EudraCT number	2013-001191-38
Trial protocol	ES
Global end of trial date	10 February 2016

Results information

Result version number	v1 (current)
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001HES01
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02040584
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,
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 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the course of kidney function from randomisation (Week 4) until the end of the study (Week 52), through the percentage of patients who show clinical benefit, by comparing an immunosuppressive regimen based on minimisation of TAC plus EVR (rTAC+EVR: study group) vs. an immunosuppressive regimen based on the combination of TAC plus MMF (TAC+MMF: control group) in de novo liver-transplant recipients. Clinical benefit is defined as:

- an improvement in 1 or 2 ranges of the eGFR, according to MDRD-4 at Week 52 post-transplant in patients with values of 30-<45 or 45-<60 mL/min/1.73 m² at randomisation.

or

- stabilization of eGFR in patients with values ≥ 60 mL/min/1.73 m² at randomisation and maintained at Week 52 post-transplant.

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	20 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 217
Worldwide total number of subjects	217
EEA total number of subjects	217

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)	173
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

291 recipients of a first liver transplant from a cadaver donor were screened, 217 patients were randomised to The safety population included all randomised patients who received at least one dose of the study medication. A total of 215 patients were included in safety population.

Pre-assignment

Screening details:

The ITT included 211 patients, 1 patient in the EVR group and 3 patients in the TAC group in the safety population were excluded due to missing MDRD-4 values after randomisation.

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	Experimental group

Arm description:

Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids

Arm type	Experimental
Investigational medicinal product name	EVR
Investigational medicinal product code	
Other name	Certican
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1.0 mg tablets (also in 0.25 and 0.5 mg tablets).

The EVR tablets should be taken whole, with a glass of water, and not broken before use. The study drug was administered in combination with corticosteroids. TAC minimisation was done, to reach trough levels (C-0h) ≤ 5 ng/mL no later than four weeks after randomisation and were maintained until Week 52 post-transplant.

Arm title	Control group
------------------	---------------

Arm description:

Treatment with TAC + MMF + corticosteroids

Arm type	Active comparator
Investigational medicinal product name	TAC
Investigational medicinal product code	
Other name	Prograf, Advagraf
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

capsules of 0.5, 1.0 and 5.0 mg

Between Weeks 2 and 3, all patients had to be in treatment with Advagraf in order to have stable levels of TAC prior to randomisation. Patients in treatment with twice-daily doses of Prograf® made the switch to Advagraf administered once daily at a 1:1 ratio (mg:mg), maintaining the total daily dose. Advagraf should be administered in the morning. During the course of the trial, the study medications were administered under a b.i.d. regimen, except for Advagraf, which was administered under a once daily regimen (s.i.d). MMF (CellCept) was provided in the form of capsules of 250-500 mg. The control arm was administered in combination with corticosteroids.

Number of subjects in period 1^[1]	Experimental group	Control group
Started	105	106
Completed	70	74
Not completed	35	32
Adverse event, serious fatal	6	3
Transplant rejection/retransplant	-	1
Adverse event, non-fatal	13	6
Unsatisfactory therapeutic effect	-	1
Immunosuppressant/prohibited med use	7	10
Protocol deviation	9	11

Notes:

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

Justification: Different population was used for the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Experimental group
-----------------------	--------------------

Reporting group description:

Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids

Reporting group title	Control group
-----------------------	---------------

Reporting group description:

Treatment with TAC + MMF + corticosteroids

Reporting group values	Experimental group	Control group	Total
Number of subjects	105	106	211
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)	77	91	168
From 65-84 years	28	15	43
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.43	55.84	
standard deviation	± 6.37	± 7.45	-
Gender, Male/Female Units: Subjects			
Female	14	16	30
Male	91	90	181

End points

End points reporting groups

Reporting group title	Experimental group
Reporting group description:	
Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids	
Reporting group title	Control group
Reporting group description:	
Treatment with TAC + MMF + corticosteroids	
Subject analysis set title	<= 14
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Experimentatl group (Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids) with MELD score <= 14	
Subject analysis set title	15 to 19
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Experimentatl group (Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids) with MELD score 15-19	
Subject analysis set title	20 to 24
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Experimentatl group (Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids) with MELD score 20 to 24	
Subject analysis set title	25 to 29
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Experimentatl group (Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids) with MELD score 25 to 29	
Subject analysis set title	> = 30
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Experimentatl group (Minimisation of TAC: Treatment with rTAC+EVR+corticosteroids) with MELD score > = 30	
Subject analysis set title	<= 14 Control group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Control group (Treatment with TAC + MMF + corticosteroids) with MELD score <= 14	
Subject analysis set title	15 to 19 Control group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Control group (Treatment with TAC + MMF + corticosteroids) with MELD score 15 to 19	
Subject analysis set title	20 to 24 Control group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Control group (Treatment with TAC + MMF + corticosteroids) with MELD score 20 to 24	
Subject analysis set title	25 to 29 Control group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Control group (Treatment with TAC + MMF + corticosteroids) with MELD score 25 to 29	
Subject analysis set title	> = 30 Control group
Subject analysis set type	Intention-to-treat

Primary: Percentages of participants showing clinical benefit by renal function startification

End point title	Percentages of participants showing clinical benefit by renal function startification
-----------------	---

End point description:

Clinical benefit is defined as: • an improvement in 1 or 2 ranges of the eGFR, according to MDRD-4 at Week 52 post-transplant in patients with values of 30-<45 or 45-<60 mL/min/1.73 m² in Week 4. or • stabilisation of eGFR in patients with values ≥60 mL/min/1.73 m² at Week 4 and maintained at Week 52 post-transplant.

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

End point timeframe:

week 4, week 52.

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Percentages of participants				
number (not applicable)				
> = 30 - 45 ml/min/1.73m ² at Week 52	4.76	3.77		
> = 45 - <60 ml/min/1.73m ² at Week 52	14.29	16.04		
> = 60 ml/min/1.73m ² at Week 52	79.05	79.25		

Statistical analyses

Statistical analysis title	Clinical Benefit by Renal Function Startification
-----------------------------------	---

Statistical analysis description:

Null hypothesis (H0): there were no differences in kidney function between the two groups, in contrast with the alternative hypothesis (H1), in which there were differences: H0: CBS = CBC versus H1: CBS ≠ CBC, where CBS and CBC were percentages of patients who showed clinical benefit at Week 52 for the study group and control group, respectively.

Comparison groups	Experimental group v Control group
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9423
Method	Fisher exact

Secondary: Changes in creatinine clearance - Cockcroft-Gault formula

End point title	Changes in creatinine clearance - Cockcroft-Gault formula
-----------------	---

End point description:

Kidney function was assessed over time by creatine clearance based on the Cockcroft-Gault formula. Estimated creatinine clearance (mL/min) = [(140 - age) x (weight) x (0.85 if female)] / (72 x serum

creatinine). Units: age (years); weight (kg); serum creatinine (mg/dL).

End point type	Secondary
End point timeframe:	
Screening visit (transplant), weeks 1,4,12,24,36 and 52 post-trasplant	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: ml/min/1.73m2				
arithmetic mean (standard deviation)				
Screening	104.67 (± 36.40)	109.69 (± 48.47)		
Week 1	116.93 (± 44.82)	118.09 (± 44.82)		
Week 4	80.19 (± 28.00)	91.26 (± 37.60)		
Week 12	87.76 (± 26.51)	90.14 (± 35.82)		
Week 24	89.57 (± 32.89)	87.93 (± 35.92)		
Week 36	94.46 (± 30.26)	90.91 (± 35.96)		
Week 52	92.21 (± 29.96)	91.04 (± 37.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in eGFR based on the MDRD-4 formula

End point title	Changes in eGFR based on the MDRD-4 formula
End point description:	
Kidney function was assessed over time by changes in eGFR according to the MDRD-4 formula. The MDRD-4 formula (Levey et al., 2000) was used based on serum concentration of creatinine (conventional units): $eGFR (mL/min/1.73 m^2) = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if of African descent})$. Units: serum creatinine (mg/dL); age (years).	
End point type	Secondary
End point timeframe:	
Screening visit (transplant), weeks 1,4,12,24,36 and 52 post-trasplant	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: ml/min/1.73m2				
arithmetic mean (standard deviation)				
Screening	100.20 (± 38.74)	99.42 (± 43.09)		
Week 1	112.86 (± 50.06)	112.15 (± 48.16)		
Week 4	82.18 (± 28.47)	88.39 (± 34.32)		
Week 12	85.99 (± 25.13)	83.57 (± 28.19)		
Week 24	86.02 (± 31.97)	82.00 (± 26.93)		
Week 36	87.68 (± 32.49)	83.04 (± 25.56)		
Week 52	86.09 (± 27.87)	83.23 (± 25.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: eGFR values(MDRD-4 formula) according to the MELD score

End point title	eGFR values(MDRD-4 formula) according to the MELD score
End point description:	
Model for End Stage Liver Disease (MELD) score: (≤ 14 , 15-19, 20-24, 25-29, ≥ 30)	
End point type	Secondary
End point timeframe:	
Screening visit (transplant), weeks 1,4,12,24,36 and 52 post-trasplant	

End point values	≤ 14	15 to 19	20 to 24	25 to 29
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	52	25	21	5
Units: ml/min/1.73m2				
median (inter-quartile range (Q1-Q3))				
Screening	96.63 (76.31 to 119.50)	90.29 (65.64 to 114.92)	88.89 (70.03 to 114.67)	104.45 (93.21 to 123.90)
Week 1	114.00 (94.24 to 142.51)	93.31 (76.61 to 127.75)	83.45 (66.76 to 114.06)	137.61 (124.30 to 148.67)
Week 4	81.37 (63.46 to 92.20)	85.19 (66.09 to 99.26)	70.57 (51.90 to 99.02)	75.94 (50.93 to 121.86)
Week 12	85.81 (64.65 to 98.87)	88.76 (65.92 to 118.20)	83.91 (68.46 to 94.96)	94.82 (50.94 to 106.28)
Week 24	80.76 (64.37 to 107.89)	81.41 (57.22 to 104.86)	78.88 (62.22 to 94.68)	84.86 (68.54 to 101.19)
Week 36	81.96 (64.82 to 111.44)	92.44 (68.05 to 113.18)	75.62 (61.64 to 100.46)	83.09 (55.72 to 110.46)

Week 52	86.14 (66.70 to 101.59)	88.94 (65.24 to 114.50)	71.60 (62.48 to 89.66)	83.94 (60.69 to 107.20)
---------	-------------------------	-------------------------	------------------------	-------------------------

End point values	> = 30	<= 14 Control group	15 to 19 Control group	20 to 24 Control group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	56	24	18
Units: ml/min/1.73m2				
median (inter-quartile range (Q1-Q3))				
Screening	38.35 (38.35 to 38.35)	102.27 (75.09 to 120.19)	93.85 (73.93 to 123.19)	91.45 (68.74 to 116.49)
Week 1	82.04 (82.04 to 82.04)	108.64 (83.22 to 138.55)	92.98 (55.41 to 129.49)	119.19 (100.53 to 147.60)
Week 4	69.43 (69.43 to 69.43)	89.44 (62.78 to 107.55)	72.76 (51.64 to 113.93)	89.67 (63.89 to 133.44)
Week 12	56.67 (56.67 to 56.67)	83.63 (69.33 to 101.35)	67.00 (48.31 to 99.84)	87.22 (67.63 to 107.01)
Week 24	60.37 (60.37 to 60.37)	80.01 (66.16 to 97.47)	70.27 (55.26 to 93.99)	82.64 (65.25 to 113.80)
Week 36	58.07 (58.07 to 58.07)	86.72 (72.09 to 97.40)	67.90 (54.34 to 90.95)	86.17 (68.59 to 107.21)
Week 52	53.93 (53.93 to 53.93)	80.92 (68.98 to 104.03)	70.32 (54.12 to 82.38)	90.66 (74.52 to 113.18)

End point values	25 to 29 Control group	> = 30 Control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: ml/min/1.73m2				
median (inter-quartile range (Q1-Q3))				
Screening	99.50 (19.76 to 137.89)	53.73 (38.82 to 66.97)		
Week 1	156.41 (29.81 to 184.87)	86.45 (57.98 to 117.96)		
Week 4	85.23 (42.83 to 109.13)	78.57 (51.47 to 108.61)		
Week 12	65.01 (43.15 to 96.53)	81.92 (58.33 to 87.43)		
Week 24	88.34 (30.17 to 104.72)	62.74 (47.46 to 75.65)		
Week 36	68.32 (57.01 to 79.63)	65.58 (45.11 to 73.55)		
Week 52	74.82 (69.00 to 80.63)	63.26 (45.52 to 79.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Urine protein/creatinine ratio

End point title	Urine protein/creatinine ratio
-----------------	--------------------------------

End point description:

The urine protein/creatinine ratio was assessed throughout follow-up in both treatment groups.

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

End point timeframe:

Screening visit, week 1,4,18,24, and 52

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: mg/g				
arithmetic mean (standard deviation)				
Screening	199.89 (± 582.03)	131.56 (± 178.95)		
Week 1	252.48 (± 308.22)	349.46 (± 396.44)		
Week 4	134.77 (± 175.05)	141.71 (± 187.11)		
Week 18	204.26 (± 688.05)	105.02 (± 79.61)		
Week 24	200.17 (± 466.55)	120.52 (± 108.04)		
Week 52	219.41 (± 406.52)	143.05 (± 220.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of proteinuria

End point title	Incidence of proteinuria
-----------------	--------------------------

End point description:

The incidence of proteinuria (≥ 0.5 - 0.9 g/day, ≥ 1.0 - 2.9 g/day and ≥ 3.0 g/day) was assessed throughout follow-up in both treatment groups. Proteinuria was defined as protein/creatinine ration ≥ 0.5 .

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

End point timeframe:

Screening visit, week 1,4,18,24, and 52

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Percentages of participants				
number (not applicable)				
≥ 0.5-1.0 g/day at screening	0.00	3.77		
≥ 1.0-3.0 g/day at screening	2.00	1.89		
≥ 3.0 g/day at screening	2.00	0.00		
≥ 0.5-1.0 g/day at Week 1	3.23	18.31		
≥ 1.0-3.0 g/day at Week 1	6.45	5.63		
≥ 3.0 g/day at Week 1	0.00	0.00		
≥ 0.5-1.0 g/day at Week 4	5.21	1.05		
≥ 1.0-3.0 g/day at Week 4	0.00	1.05		
≥ 3.0 g/day at Week 4	0.00	0.00		
≥ 0.5-1.0 g/day at Week 18	0.00	0.00		
≥ 1.0-3.0 g/day at Week 18	1.39	0.00		
≥ 3.0 g/day at Week 18	1.39	0.00		
≥ 0.5-1.0 g/day at Week 24	7.58	1.52		
≥ 1.0-3.0 g/day at Week 24	0.00	0.00		
≥ 3.0 g/day at Week 24	1.52	0.00		
≥ 0.5-1.0 g/day at Week 52	6.67	1.89		
≥ 1.0-3.0 g/day at Week 52	3.33	1.89		
≥ 3.0 g/day at Week 52	0.00	0.00		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of patients with acute rejection, BPAR, and treated BPAR

End point title	Incidence of patients with acute rejection, BPAR, and treated BPAR
-----------------	--

End point description:

Liver biopsy had to be performed in all cases where acute rejection was suspected. Results of the biopsy were interpreted by the local pathologist (who did not know the treatment given to the patient) according to the Banff classification (1997). Biopsy-proven acute rejection (BPAR) defined as clinical suspicion of acute rejection confirmed in biopsy. Treated BPAR was deemed to be an episode of acute rejection in which the interpretation of the local pathologist showed that it reached any grade of acute rejection under the Banff classification, and for which anti-rejection therapy was administered. Loss of the liver allograft was deemed to have occurred the day that the patient was again included on the waiting list for liver transplant, the day he or she received another allograft or upon the death of the patient. All suspected hepatic allograft rejections were considered acute rejection

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

End point timeframe:

Throughout the study period, approximately 3 years

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Percentages of participants				
number (not applicable)				
Patients with suspected acute rejection	17.14	15.09		
Patients with BPAR	5.71	3.77		
Patients with treated BPAR	4.76	1.89		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to rejection

End point title	Time to rejection
End point description:	
Time to acute rejection was calculated from the date of transplantation. Acute rejection date was taken from biopsy date, as the date of rejection was not collected. Time to treated BPAR was calculated from the date of transplantation.	
End point type	Secondary
End point timeframe:	
Throughout study period, approximately 3 years	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: months				
arithmetic mean (standard deviation)				
Time to acute rejection	3.74 (± 3.15)	2.91 (± 2.89)		
Time to treated BPAR	2.65 (± 1.50)	3.85 (± 5.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of rejection

End point title	Severity of rejection
End point description:	
Severity of acute rejection and treated BPAR was graded according to Banff criteria. Severity grade: mild, moderate, severe.	
End point type	Secondary
End point timeframe:	
Throughout study period, approximately 3 years	

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Percentages of participants				
number (not applicable)				
Severity of acute rejection: Mild (Grade I)	13.64	11.11		
Severity of acute rejection: Moderate(Grade II)	13.64	5.56		
Severity of acute rejection: Severe(Grade III)	0.00	5.56		
Severity of treated BPAR: Mild (Grade I)	33.33	0.00		
Severity of treated BPAR: Moderate(Grade II)	50.00	50.00		
Severity of treated BPAR: Severe(Grade III)	0.00	50.00		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of participants with HCV-positive and HCV genotype

End point title	Percentages of participants with HCV-positive and HCV genotype
End point description:	The viral load of HCV-RNA and HCV genotype (describing the genotypes present) was assessed in HCV-positive patients.
End point type	Secondary
End point timeframe:	approximately 3 years

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Percentages of participants				
number (not applicable)				
Hepatitis C virus (HVC) positive	33.33	36.79		
HCV genotypic 01	80.00	76.92		
HCV genotype 02	0.00	0.00		
HCV genotype 03	17.14	10.26		
HCV genotype 04	2.86	2.56		
HCV genotype 05	0.00	0.00		
HCV genotype 06	0.00	0.00		

HCV genotype 07	0.00	0.00		
non-responders	0.00	10.26		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of p-P70S6K

End point title	Concentration of p-P70S6K ^[1]
-----------------	--

End point description:

the biomarker of personal response to everolimus, monitoring of the activity of the target, kinase P70 S6, in its total and phosphorylated form at Thr389

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

End point timeframe:

week 6,8,12,18,24,36,52

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: no statistical analyses done for this endpoint.

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: ng/ml				
arithmetic mean (standard deviation)				
Cmin EVR week 6	3.8 (± 1.7)			
C1h EVR week 6	6.8 (± 6.3)			
Cmin EVR week 8	4.7 (± 1.6)			
C1h EVR week 8	9.5 (± 4.9)			
Cmin EVR week 12	4.4 (± 1.8)			
C1h EVR week 12	16 (± 9.5)			
Cmin EVR week 18	6.8 (± 2.7)			
C1h EVR week 18	14.6 (± 6.7)			
Cmin EVR week 24	5.3 (± 2.13)			
C1h EVR week 24	18 (± 7.2)			
Cmin EVR week 36	5.1 (± 1.35)			
C1h EVR week 36	12.7 (± 4.2)			
Cmin EVR week 52	5.35 (± 0.97)			
C1h EVR week 52	16.1 (± 7.6)			

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	19.0

Reporting groups

Reporting group title	Experimental group
-----------------------	--------------------

Reporting group description:

Experimental group

Reporting group title	Control group
-----------------------	---------------

Reporting group description:

Control group

Serious adverse events	Experimental group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 106 (51.89%)	48 / 109 (44.04%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			

subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of thorax			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland neoplasm			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial stenosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Steal syndrome			

subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bile duct stent removal			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	0 / 106 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	6 / 106 (5.66%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	1 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular cyst			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular disorder			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic paralysis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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	1 / 106 (0.94%)	0 / 109 (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	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Product issues			
Device ineffective			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy liver			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	4 / 106 (3.77%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laboratory test			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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			
Anastomotic stenosis			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
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	0 / 106 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted liver			
subjects affected / exposed	3 / 106 (2.83%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver graft loss			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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	4 / 106 (3.77%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transplant dysfunction subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhagic stroke			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 106 (1.89%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 106 (1.89%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukopenia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 106 (2.83%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			

subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	3 / 106 (2.83%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 106 (1.89%)	0 / 109 (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	1 / 106 (0.94%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Duodenal ulcer			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	1 / 106 (0.94%)	0 / 109 (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	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	3 / 106 (2.83%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			

subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	4 / 106 (3.77%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract disorder			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Budd-Chiari syndrome			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	2 / 106 (1.89%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	2 / 106 (1.89%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation intrahepatic duct acquired			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery stenosis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery thrombosis			
subjects affected / exposed	2 / 106 (1.89%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	1 / 106 (0.94%)	0 / 109 (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 / 106 (0.00%)	1 / 109 (0.92%)	
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	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jaundice			
subjects affected / exposed	0 / 106 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jaundice cholestatic			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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			
Pruritus generalised			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	2 / 106 (1.89%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	2 / 106 (1.89%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular disorder			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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			
Musculoskeletal pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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 sepsis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abscess			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
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	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus oesophagitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 106 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	6 / 106 (5.66%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 106 (0.94%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 106 (1.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (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	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	5 / 106 (4.72%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 106 (1.89%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 106 (1.89%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 106 (91.51%)	105 / 109 (96.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 106 (22.64%)	26 / 109 (23.85%)	
occurrences (all)	27	28	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	11 / 106 (10.38%)	16 / 109 (14.68%)	
occurrences (all)	11	19	
Oedema			
subjects affected / exposed	8 / 106 (7.55%)	5 / 109 (4.59%)	
occurrences (all)	8	6	
Oedema peripheral			
subjects affected / exposed	39 / 106 (36.79%)	27 / 109 (24.77%)	
occurrences (all)	52	32	
Pyrexia			
subjects affected / exposed	15 / 106 (14.15%)	17 / 109 (15.60%)	
occurrences (all)	19	22	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	15 / 106 (14.15%)	17 / 109 (15.60%)	
occurrences (all)	16	17	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 106 (6.60%)	3 / 109 (2.75%)	
occurrences (all)	8	3	
Insomnia			
subjects affected / exposed	17 / 106 (16.04%)	10 / 109 (9.17%)	
occurrences (all)	17	10	
Investigations			
Transaminases increased			
subjects affected / exposed	9 / 106 (8.49%)	6 / 109 (5.50%)	
occurrences (all)	9	6	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 106 (10.38%)	12 / 109 (11.01%)	
occurrences (all)	13	19	
Tremor			
subjects affected / exposed	13 / 106 (12.26%)	19 / 109 (17.43%)	
occurrences (all)	14	23	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	30 / 106 (28.30%)	36 / 109 (33.03%)	
occurrences (all)	32	39	
Leukocytosis			
subjects affected / exposed	6 / 106 (5.66%)	7 / 109 (6.42%)	
occurrences (all)	8	7	
Leukopenia			
subjects affected / exposed	14 / 106 (13.21%)	10 / 109 (9.17%)	
occurrences (all)	16	10	
Neutropenia			
subjects affected / exposed	4 / 106 (3.77%)	12 / 109 (11.01%)	
occurrences (all)	4	14	
Thrombocytopenia			
subjects affected / exposed	24 / 106 (22.64%)	22 / 109 (20.18%)	
occurrences (all)	27	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 106 (7.55%)	11 / 109 (10.09%)	
occurrences (all)	11	12	
Abdominal pain upper			
subjects affected / exposed	6 / 106 (5.66%)	3 / 109 (2.75%)	
occurrences (all)	6	3	
Ascites			
subjects affected / exposed	24 / 106 (22.64%)	17 / 109 (15.60%)	
occurrences (all)	28	18	
Constipation			
subjects affected / exposed	13 / 106 (12.26%)	7 / 109 (6.42%)	
occurrences (all)	14	10	
Diarrhoea			
subjects affected / exposed	20 / 106 (18.87%)	29 / 109 (26.61%)	
occurrences (all)	28	36	
Ileus paralytic			
subjects affected / exposed	2 / 106 (1.89%)	8 / 109 (7.34%)	
occurrences (all)	2	8	
Vomiting			

subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 9	14 / 109 (12.84%) 15	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	22 / 106 (20.75%)	19 / 109 (17.43%)	
occurrences (all)	23	20	
Jaundice			
subjects affected / exposed	2 / 106 (1.89%)	6 / 109 (5.50%)	
occurrences (all)	2	6	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 106 (8.49%)	8 / 109 (7.34%)	
occurrences (all)	9	10	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 106 (4.72%)	6 / 109 (5.50%)	
occurrences (all)	5	6	
Proteinuria			
subjects affected / exposed	11 / 106 (10.38%)	2 / 109 (1.83%)	
occurrences (all)	12	2	
Renal failure			
subjects affected / exposed	12 / 106 (11.32%)	16 / 109 (14.68%)	
occurrences (all)	12	17	
Renal impairment			
subjects affected / exposed	9 / 106 (8.49%)	16 / 109 (14.68%)	
occurrences (all)	11	19	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 106 (16.04%)	13 / 109 (11.93%)	
occurrences (all)	19	15	
Infections and infestations			
Hepatitis C			
subjects affected / exposed	6 / 106 (5.66%)	4 / 109 (3.67%)	
occurrences (all)	6	4	
Urinary tract infection			

subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 6	8 / 109 (7.34%) 10	
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 4	6 / 109 (5.50%) 6	
Decreased appetite			
subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 4	6 / 109 (5.50%) 7	
Diabetes mellitus			
subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 6	13 / 109 (11.93%) 15	
Dyslipidaemia			
subjects affected / exposed occurrences (all)	11 / 106 (10.38%) 11	2 / 109 (1.83%) 2	
Hypercholesterolaemia			
subjects affected / exposed occurrences (all)	13 / 106 (12.26%) 13	8 / 109 (7.34%) 8	
Hyperglycaemia			
subjects affected / exposed occurrences (all)	16 / 106 (15.09%) 18	17 / 109 (15.60%) 18	
Hyperkalaemia			
subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2	6 / 109 (5.50%) 7	
Hypertriglyceridaemia			
subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 6	7 / 109 (6.42%) 7	
Hypomagnesaemia			
subjects affected / exposed occurrences (all)	5 / 106 (4.72%) 6	9 / 109 (8.26%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2013	The Ethics Reference Committee requested clarifications and changes regarding General-ICF and Biomarkers Substudy-ICF. These changes were included in the Protocol version submitted to Heath Authorities.
03 September 2013	Calculation of eGFR formula (CKD-EPI) was added Information about the pathology at transplant was grouped according to patients with hepatocellular carcinoma (HCC) or without HCC Some changes in biochemistry parameters and urine analysis were added.
31 March 2014	HCC diagnosis will be obtained at the inclusion of patient on the waiting list. Some changes in the treatment of patients with hepatitis C were added. Some changes in prohibited medication were implemented. Determination of P70-S6 and cytokines will be done after administration of (15 ml) and 1h after de administration of 15 ml, whenever possible. Infections will be registered in the CRF Infections registry (not in the AEs registry). Weight will not only be determined at screening, also at baseline if conditions permit. Some changes in hematology and biochemistry parameters were added.
30 May 2014	Randomisation visit (change in the window period). Change in inclusion criteria for randomisation.
19 November 2014	Some clarifications were done related to: -The randomisation window period -The recommendation that blood trough levels should be obtained at 5 ± 2 days after a dose change, both for TAC and EVR. -The dose reduction of TAC (experimental group) will be maintained to be performed within 4 weeks post-randomisation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported