



## Clinical trial results:

**A controlled, randomized, assessor blinded, open-label study to investigate whether initiation of everolimus will reduce the incidence of developing a new Squamous Cell Carcinoma (SCC) and other malignancies in Renal Transplanted Recipients with at least one SCC during the last 2 years**

### Summary

EudraCT number	2012-005481-35
Trial protocol	DK
Global end of trial date	21 April 2015

### Results information

Result version number	v1
This version publication date	10 September 2016
First version publication date	10 September 2016

### Trial information

#### Trial identification

Sponsor protocol code	2012-005481-35
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	Sjukhusvägen, Uppsala, Sweden, 75185
Public contact	Andre Western, Smerud Medical Research, 0047 90526246, andre.western@smerud.com
Scientific contact	Andre Western, Smerud Medical Research, 0047 90526246, andre.western@smerud.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	01 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 April 2015
Global end of trial reached?	Yes
Global end of trial date	21 April 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to investigate whether initiation of everolimus and discontinuation/ minimization of calcineurin inhibitors (CNI) in maintenance renal transplant patients with at least one earlier diagnosed SCC incident within the last two years prior to inclusion, will reduce the risk of new SCC incidents (per definition, SCC includes SCC in situ (Mb Bowen) and keratoacanthoma (KA) like SCC).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to withdraw at any time. Patients were treated in the clinic with standard care for this population.

Background therapy:

No treatments that were not test or comparator products was used across the two arms in the trial.

Evidence for comparator:

Patients in the control arm continued their standard immunosuppressive regimen, i.e. CNI, +/- MPA, +/- steroids, +/- AZA.

Actual start date of recruitment	04 June 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	Sweden: 11
Country: Number of subjects enrolled	Denmark: 9
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	5
From 65 to 84 years	15
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All subjects who signed the ICF and entered the formal screening process were assigned a unique patient number automatically via the eCRF system. On Day 1 (preferably both screening and randomization day) the patients were randomized, in a 1:1 ratio, to one of the treatment groups according to a randomization list generated by the statistician.

### Pre-assignment

Screening details:

Male or female kidney transplant recipients aged 18 years or older.

Patient transplanted at least 12 months prior to enrolment.

Patient had experienced at least one SCC within the last 2 years.

Patients receiving a standard immunosuppressive treatment with CNI, +/- MPA, +/- steroids and/or +/- AZA

### Period 1

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

Blinding implementation details:

The pathologist assessing the biopsy will be blinded to treatment arm.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Controll

Arm description:

Standard immunosuppressive regimen with CNI

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus/cyclosporine
Investigational medicinal product code	L04AD
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Per patient standard dose of Tacrolimus given QD per patient standard, or cyclosporin given BID

<b>Arm title</b>	Everolimus
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Arm description:

Patients randomized to the everolimus arm received study drug twice a day corresponding to a blood trough level of 6-10 ng/mL. The CNI was down-titrated and finally stopped on Day 28.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	L04AA
Other name	Certican
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Up-titration to reach a blood trough level of 6-10 ng/mL at Day 28

<b>Number of subjects in period 1</b>	Controll	Everolimus
Started	6	14
Completed	0	0
Not completed	6	14
Sponsor stopped study	6	14

## Baseline characteristics

### Reporting groups

Reporting group title	Control
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Reporting group description:

Standard immunosuppressive regimen with CNI

Reporting group title	Everolimus
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Reporting group description:

Patients randomized to the everolimus arm received study drug twice a day corresponding to a blood trough level of 6-10 ng/mL. The CNI was down-titrated and finally stopped on Day 28.

Reporting group values	Control	Everolimus	Total
Number of subjects	6	14	20
Age categorical			
Of the 20 randomized subjects, 8 subjects were randomized to the control arm and 12 to the everolimus arm. However, two subject in the control arm were given everolimus due to a misunderstanding in the randomization process. These two subjects are included in the everolimus arm in the report, hence there are 6 subjects in the control arm and 14 in the everolimus arm.			
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)	0	5	5
From 65-84 years	6	9	15
85 years and over	0	0	0
Gender categorical			
Female			
Units: Subjects			
Female	1	5	6
Male	5	9	14

## End points

### End points reporting groups

Reporting group title	Controll
Reporting group description: Standard immunosuppressive regimen with CNI	
Reporting group title	Everolimus
Reporting group description: Patients randomized to the everolimus arm received study drug twice a day corresponding to a blood trough level of 6-10 ng/mL. The CNI was down-titrated and finally stopped on Day 28.	

### Primary: Propotion of patients who develop one new SCC while in the trial

End point title	Propotion of patients who develop one new SCC while in the trial
End point description:	
End point type	Primary
End point timeframe: Baseline, Month 24.	

End point values	Controll	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: Number of new SCC	3	2		

### Statistical analyses

Statistical analysis title	Not done
Statistical analysis description: NA	
Comparison groups	Controll v Everolimus
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	≤ 0.05 <sup>[2]</sup>
Method	Fisher exact

Notes:

[1] - Analysis not performed because the study was stopped prematurely.

[2] - Analysis not performed because the study was stopped prematurely.

### Secondary: Days to first SCC per group since last SCC

End point title	Days to first SCC per group since last SCC
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End point description:

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End point type	Secondary
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End point timeframe:

Baseline, Month 24

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<b>End point values</b>	Controll	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: Days to first SCC	71	177		

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline, Month 24

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Control
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Reporting group description: -

Reporting group title	Everolimus
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Reporting group description: -

Serious adverse events	Control	Everolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	5 / 14 (35.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Ileus	Additional description: DOB: 1936, Male, Control Group (cyclosporine). Randomized on 12Nov2014. Hospitalized on 08Nov2014 due to abdominal pain, while in the screening period. CT abdomen was performed which verified ILEUS.		
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: DOB: 1949, Female, Everolimus Group. First dose of study drug given 08Oct2014. The patient experience diarrhea and was hospitalized on 18Dec2014 due to dehydration. SUSPECTED relationship to study medication.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Additional description: DOB: 1939, Female, DOB: 1939 Male: Everolimus Group. Both treated in the out-patient clinic for suspected pneumonia. HRCT showed bilateral infiltrates, and diagnosed with PNEUMONITIS. Both SUSPECTED relationship to study drug.		
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary retention	Additional description: DOB: 1938, Male, Everolimus Group. First dose of study drug given 01Dec2014. The patient had Benign prostatic hyperplasia (BPH) since 2012. Hospitalized (start 03Mar2015) and an ultrasound showed residual urine > 300 mL after insertion of a KAD.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism tertiary	Additional description: DOB: 1939, Female, Everolimus Group. Last dose of study drug was given on 27May2014 and tacrolimus re-started. The patient was hospitalized late October 2014 with the diagnosis Tertiary hyperparathyroidism.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis novovirus	Additional description: DOB: 1941, Male, Everolimus Group. This event was stated as due to an epidemic and diagnosed as a Novovirus infection, judged as not related to study medication.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis	Additional description: DOB: 1949, Female, Everolimus Group. First dose of study drug given 08Oct2014. Colon biopsy, taken 13Jan2015, verified Cytomegalovirus colitis. Hospitalized on 24Feb2015 starting treatment with Cymevene. SUSPECTED relationship to everolimus.		
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
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: 0 %

Non-serious adverse events	Control	Everolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	14 / 14 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

Fatigue subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 14 (14.29%) 2	
Feeling cold subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Malaise subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Oedema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 14 (0.00%) 0	
Psychiatric disorders Restlessness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Investigations Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 14 (21.43%) 4	
Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 14 (21.43%) 3	
Haemoglobin increased			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 14 (14.29%) 2	
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Oral mucosal blistering subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2	
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2	
Pruritus subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 14 (14.29%) 2	
Skin fissures subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Urticaria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 14 (7.14%) 1	
Renal and urinary disorders			

Albuminuria			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Oral fungal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Oral infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 14 (35.71%)	
occurrences (all)	0	6	
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			

subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	3	
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Increased insulin requirement			
subjects affected / exposed	0 / 6 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2013	The rationale for the amendment was comments from the Swedish Medicinal Products Agency in connection with their 30-day response. Changes were mainly tighter inclusion/exclusion criteria. Also measurements of AST/ALT were added in order to evaluate liver function, and urine glucose was to detect possible side effects of Certican.
26 May 2014	The amendment was made because the study changed sponsor from Oslo University Hospital, Norway, to Uppsala University Hospital, Sweden.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 April 2015	<p>After 1.5 years of patient recruitment the scientific steering committee of the study evaluated the study and drew the conclusion that the study had to be terminated prematurely. This was based solely on futility, i.e. the committee could not see it possible to recruit sufficient number of patients in order to reach the goal of the study within a reasonable time frame. Further, an evaluation of involvement of other countries was done, but it was considered not possible to obtain the same local financial support as achieved in Scandinavia, and therefore, such an alternative was rejected.</p> <p>The discussion within the steering committee furthermore clarified that the reasons for futility was different among countries and regions. In Norway, a huge proportion of patients had already been converted to everolimus, whereas this situation was different in Denmark and Sweden. On the other hand, several patients in Denmark had actually declined participation, simply as they (presumably were pleased with their current medication and) did not wish to risk being converted.</p> <p>Due to the decision of prematurely terminate the study, all patients were taken in for a final study visit.</p>	-

Notes:

### Limitations and caveats

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

The study was stopped after inclusion of 20 patients due to futility. This means that the planned statistical analysis could not be performed as planned. Data are presented as listings only.

Notes: