



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 |
|-----------------------|----------------|

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 |
| Arm title | 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

| | |
|------------------|------------|
| Arm title | Everolimus |
|------------------|------------|

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

| Number of subjects in period 1 | 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 |
|-----------------------|---------|

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.

| 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 ^[1] |
| P-value | ≤ 0.05 ^[2] |
| 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 |
|-----------------|--|

End point description:

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

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: Days to first SCC | 71 | 177 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline, Month 24

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

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

Reporting group description: -

| | |
|-----------------------|------------|
| Reporting group title | Everolimus |
|-----------------------|------------|

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