A 24 month, multicenter, randomized, open-label safety and efficacy study of concentration-controlled everolimus with reduced calcineurin inhibitor vs mycophenolate with standard calcineurin inhibitor in de novo renal transplantation- Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen (TRANSFORM)

Published: 13-11-2013
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Primary: to evaluate the effect of everolimus with reduced exposure CNI versus MPA with standard exposure CNI on the binary composite of treated biopsy-proven acute rejection (tBPAR) or eGFR < 50mL/min/1.73m2 at Month 12 post-transplantation.Key...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44739

Source
ToetsingOnline

Brief title
TRANSFORM

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
rejection after kidney transplantation

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: everolimus, kidney, TRANSFORM, transplantation

Outcome measures

Primary outcome

Treated biopsy-proven acute rejection (tBPAR), eGFR < 50 mL/min/1.73m2 at Month

12 post-transplantation.

Secondary outcome

Efficacy failure rate (tBPAR, graft loss or death).

Study description

Background summary

In renal transplant patients, chronic allograft nephropathy (interstitial fibrosis and tubular atrophy) is the main cause of graft failure. Calcineurin-inhibitors (CNI*s) represent the cornerstone of immunosuppressive therapy due to their efficacy in preventing acute rejection. However, CNIs have

nephrotoxic side effects that can directly contribute to renal dysfunction and compromise long-term outcomes.
Several reports have shown that improvements in graft half-life are related to conservation of renal function within the first-year post-transplantation.
Therefore, treatment strategies that allow adequate immunosuppression to control rejection, avoid nephrotoxicity and improve long-term outcomes are sought.
The de novo use of everolimus with CNI minimization provides an opportunity to manage the risk of acute allograft rejection, reduce exposure to CNI nephrotoxicity without compromising efficacy and potentially provide long-term benefits. Studies show that a regimen with de novo everolimus and CNI minimization is at least as effective as standard CNI-based regimens in terms of patient and allograft survival rates, with some improvements in renal function.
The present study builds on existing evidence and, with an innovative novel endpoint, combining renal function and allograft rejection, aims to demonstrate that de novo concentration-controlled everolimus, plus very low levels of CNI, will lead to better overall graft outcomes, as compared to current standard of care, being Mycophenolic acid (MPA) plus standard dose CNI.

Study objective

Primary: to evaluate the effect of everolimus with reduced exposure CNI versus MPA with standard exposure CNI on the binary composite of treated biopsy-proven acute rejection (tBPAR) or eGFR < 50 mL/min/1.73m2 at Month 12 post-transplantation.
Key secondary: To evaluate everolimus with reduced exposure CNI compared to MPA plus standard exposure CNI at 12 months post-transplantation with respect to the composite efficacy failure rate (tBPAR, graft loss or death). To evaluate the binary composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m2 (MDRD4) Month 12 among compliant subjects.
Full listing of objectives: see protocol page 15-16.

Study design

Randomized, open-label phase IV study.
Randomization (1:1) to
* Everolimus plus low dose Tacrolimus or Cyclosporine
* Mycophenolic acid plus standard dose Tacrolimus or Cyclosporine.
Treatment duration approx. 2 years.
2040 patients.

Intervention

Treatment with everolimus plus low dose Tacrolimus or Cyclosporine or treatment

with Mycophenolic acid plus standard dose Tacrolimus or Cyclosporine.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Study duration approx. 2 years. Approx. 13 visits (1-2 h).
Physical examination yearly.
Blood and urine tests every visit. Approx. 6 ml blood per occasion extra compared to standard treatment, approx. 100 ml in total.
Pregnancy test every 6 months.
Kidney biopsy if medically indicated.
Optional tests: kidney biopsy (every year, NOT in NL), blood tests for antibodies (yearly, 5 ml blood per occasion).

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Male and female patients, * 18 years of age.
* Randomized within 24 hr of completion of transplant surgery.
* Cold ischemia time < 30 hr.
* Primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased heart beating, living unrelated, living related non-human leukocyte antigen identical or an expanded criteria donor.

Exclusion criteria

* Multi-organ transplant recipient.
* High immunological risk for rejection.
* BMI >35.
* Severe systemic infections, current or within the two weeks prior to randomization.
* Systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy.
* Pregnant or lactating women.
* Women of child-bearing potential not using adequate contraception.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-03-2014
Enrollment:	130

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Certican
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Neoral
Generic name:	cyclosporime
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prograft
Generic name:	tacrolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-11-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-12-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-01-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-02-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	clinicaltrials.gov; NCT01950819
EudraCT	EUCTR2013-000322-66-NL
CCMO	NL46728.058.13