A partially-blinded, active-controlled, multicenter, randomized study evaluating efficacy, safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of an anti-CD40 monoclonal antibody, CFZ533, in de novo and maintenance kidney transplant recipients (CIRRUS I, CCFZ553A2201)

Published: 06-07-2018
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Primary Objective(s) (Cohort 1):* To demonstrate that CFZ533 600 mg and/or 300 mg bi-weekly (Q2W), subcutaneous (SC), is non-inferior to a tacrolimus-based regimen with respect to the proportion of patients who experience composite efficacy failure…

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

Summary

ID

NL-OMON55663

Source
ToetsingOnline

Brief title
CIRRUS I

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
kidney transplantation

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: anti-CD40, kidney transplantation

Outcome measures

Primary outcome

Primary study parameters/outcome of the study:

Composite efficacy (BPAR, Graft Loss or Death)

BPAR (Banff grade)

tBPAR

AR

tAR

Graft Loss

Death

Graft Loss + Death

Total Banff score

Renal function (eGFR)

Proportion of patients with AEs, SAEs, AEs related to study drug

AEs of special interest: infections, malignancies, including PTLD,

thromboembolic events, MACE, NODM

Secondary outcome

CFZ533 plasma concentrations over time (Cmax, Ctrough, AUC)

Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (immunogenicity).

Immunophenotyping.

iBox risk prediction score

total Banff score

Chronic Allograft Damage Index (CADI)

De novo DSA

PROs (SF-36 and MTSOSD)

Biomarkers

Study description

Background summary

The purpose of this study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of:

- two CFZ533 dose regimens in de novo kidney transplant recipients, in combination with mycophenolate mofetil (MMF) and corticosteroids, compared to a standard of care control arm of tacrolimus, MMF and corticosteroids.

- one CFZ533 dose regimen started 6-24 months post-transplantation in maintenance kidney transplant recipients, in combination with either MMF or EC-MPS with or without corticosteroids, compared to a standard of care control arm of tacrolimus and MMF or EC-MPS with or without corticosteroids.

This study will allow the assessment of the ability of CFZ533 to replace CNIs as the standard of care by potentially improving long term outcome (reduced graft loss) while maintaining comparable short term anti-rejection efficacy, and providing better renal function with an adequate safety and tolerability

profile, in de novo and maintenance renal transplant patients.

Study objective

Primary Objective(s) (Cohort 1):
* To demonstrate that CFZ533 600 mg and/or 300 mg bi-weekly (Q2W), subcutaneous (SC), is non-inferior to a tacrolimus-based regimen with respect to the proportion of patients who experience composite efficacy failure event (biopsy proven acute rejection (BPAR), graft loss, or death) over 12 months post-transplantation.

Secondary objective (Cohort 1):
* To demonstrate that CFZ533 600 mg and/or 300 mg Q2W SC are superior to a tacrolimus-based regimen with respect to the mean estimated glomerular filtration rate (eGFR) over 12 months post-transplantation.
* To assess the safety and tolerability of CFZ533 regimens compared to a TAC based-regimen.
* To assess the pharmacokinetics of CFZ533 and explore the dose-exposure relationship during the 60 months treatment period.
* To assess the immunogenicity of CFZ533 during the 60 months treatment period.

Primary Objective(s) (Cohort 2):
* To demonstrate that CFZ533 450 mg bi-weekly (Q2W) subcutaneously (SC) is non-inferior to a tacrolimus-based regimen with respect to the proportion of patients who experience composite efficacy failure event (biopsy proven acute rejection (BPAR), graft loss, or death) over 12 months post conversion

Secondary Objective(s) (Cohort 2):
* To demonstrate that CFZ533 450 mg Q2W SC is superior to a tacrolimus-based regimen with respect to the mean change in eGFR from baseline over 12 months post conversion.
* To assess the safety and tolerability of CFZ533 regimen compared to a TAC-based regimen.
* To assess the pharmacokinetics of CFZ533 during the 60 months treatment period and explore the dose-exposure relationship (together with PK data from Cohort 1).
* To evaluate the immunogenicity of CFZ533 during the 60 months treatment period.

Study design

Study CCFZ533A2201 is a randomized, 60-month, (5 year) study comprising of 12-months treatment for the primary analysis plus an additional 48-month treatment period. The study is active-controlled, partially-blinded, for the initial 12 months of treatment, multicenter, dose range finding study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 in 2 different

cohorts:

In adult de novo kidney transplant recipients, CFZ533 in combination with MMF and corticosteroids as compared to standard of care comprised of tacrolimus, MMF and corticosteroids.

In a maintenance kidney transplant population (6-24 months post-transplant), CFZ533 in combination with MMF with or without corticosteroids, compared to a standard of care control arm of tacrolimus and MMF with or without corticosteroids.

Intervention

Cohort 1 * de novo patients:

Arm 1: CFZ533 30 mg/kg IV (Day 1), CFZ533 15 mg/kg IV (Day 5), then CFZ533 600 mg SC Q2W (from Day 15) + MMF + corticosteroids (n=75)

Arm 2: CFZ533 30 mg/kg IV (Day 1), CFZ533 15 mg/kg IV (Day 5), then CFZ533 300 mg SC Q2W (from Day 15) CFZ533 + MMF + corticosteroids (n=75)

Arm 3: TAC + MMF + corticosteroids (n=50). All patients will receive induction therapy: Basiliximab or Thymoglobulin (rATG)

Cohort 2 * maintenance patients:

Arm 1: CFZ533 30 mg/kg IV (Day 1) then CFZ533 450 mg SC Q2W (from Day 15) + MMF/EC-MPS ± corticosteroids (n=75)

Arm 2: TAC + MMF/EC-MPS ± corticosteroids (n=50)

Study burden and risks

Duration of study: 5 year, 31 hospital visits, 93 home administrations.
Blood pressure, pulse, temperature: 31x
Blood and urine examination at every (hospital) visit
Pregnancy test every hospital visit and every month at home
Kidney biopsy on D1 (back-table) in cohort 1; D1 cohort 2 (if biopsy is not available in month prior to D1); Month 12, Month 60/End of Study and if medically required (in case of a suspected rejection).
ECG 20x
Questionnaires (1 à 2): 3x

Contacts

Public
Novartis

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NL
Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patient * 18 years old.
- Up to date vaccination
- Recipients of a primary kidney transplant from a brain-death donor (DBD), living unrelated or non-HLA identical living related donor (cohort1).
- Recipients of a kidney with a cold ischemia time (CIT) <24 hours (cohort 1)
- Recipients of a primary graft received 6 to 24 months prior enrollment, on a regimen containing Tac+MMF/EC-MPS±CS (Cohort 2)
- Patients with an actual eGFR according to Modification of Diet in Renal Disease (MDRD-4) * 45 mL/min/1.73m2 (Cohort 2)

Exclusion criteria

- Multi-organ transplant recipients including en bloc and dual kidney transplantation or prior kidney transplant (cohort 1 and 2)
- Pregnant or nursing women (cohort 1 and 2)
- Women of child bearing potential unless using highly effective methods of contraception during dosing and 12 weeks after study medication has been stopped (cohort 1 and 2)
- Recipients of an organ from a donor after cardiac death (DCD) (cohort 1).
- Recipient of an organ from an HLA identical living related donor (cohort 1).
- Recipients of kidneys from donors who are older than 65 years (cohort 1).
- Patients at high immunological risk for rejection (cohort 1)
- DSA within 12 weeks prior enrollment (cohort 2)
- Ongoing rejection or rejection that required treatment within 12 weeks prior enrollment (cohort 2)
- Severe humoral and/or cellular rejection (BANFF * IIb) within 12 weeks before enrollment (cohort 2)
- Recipient of a kidney from a donor who tests positive for HIV, HBsAg or HCV (cohort 1)
- Patients who weigh less than 30kg or more than 180kg (cohort 1 and 2)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-01-2019
Enrollment:	35

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CFZ533
Generic name:	Iscalimab

Ethics review

Approved WMO Date:	06-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2017-003607-22-NL

Register	ID
ClinicalTrials.gov	NCT03663335
CCMO	NL66119.078.18