A 12-month randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of an anti-CD40 monoclonal antibody, CFZ533, in combination with mycophenolate mofetil (MMF) and corticosteroids (CS), with and without tacrolimus (Tac), in de novo renal transplant recipients

Published: 25-11-2015
Last updated: 19-04-2024

Primary:Part 1: PK, PD and SafetyTo assess the safety, tolerability and pharmacokinetics of multiple IV and SC doses of CFZ533 in combination with MMF, CS, and Tac (standard exposure) in de novo renal transplant patients over the treatment and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45886

Source
ToetsingOnline

Brief title
CCFZ533X2201

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. (de sponsor/verrichter van het onderzoek)

Intervention

Keyword: anti-CD40, kidney transplantation

Outcome measures

Primary outcome

* Treated biopsy proven acute rejection (tBPAR), graft loss, death, estimated

GFR

* Renal function

* Adverse and serious adverse events

* Infections

* Cytokines

* Donor specific antibodies

* NODAT

* EBV, CMV and BK virus and tuberculosis surveillance

* Viral serology

* Immunogenicity

* ECG

* Vital signs

* Clinical labs

Secondary outcome

* Pharmacokinetics:

* Free CFZ533 in plasma

* Tac trough levels

* MPA trough levels

* Pharmacodynamics:

* Peripheral blood CD40 receptor occupancy (free CD40, total CD40 on B cells)

* Immunophenotyping

* Soluble CD40 and soluble CD154 in plasma

* Graft survival

* Patient survival

* Lymph node / tissue biopsy

* Renal biomarkers

* Pharmacogenetics

* Pharmacogenomics

Study description

Background summary

The purpose of this adaptive, two-part study is to investigate the potential for CFZ533 to replace calcineurin inhibitors (CNI), while providing a similar rate of acute rejection prophylaxis and better renal function in a de novo renal transplant population receiving an allograft from standard criteria donors.

Part 1 of this trial will focus on profiling the multiple dose pharmacokinetics (PK), pharmacodynamics (PD) and tolerability for both IV and SC CFZ533 administration in the setting of standard-of-care, CNI-based immunosuppression.

Part 2 will evaluate the safety and efficacy of CFZ533 in the absence of a CNI in combination with adjunct MMF and basiliximab induction therapy for up to 12 months. Overall, results of this study will be used to inform the CFZ533 dose and regimen selection for investigation in later phases of clinical development.

Study objective

Primary:
Part 1: PK, PD and Safety
To assess the safety, tolerability and pharmacokinetics of multiple IV and SC doses of CFZ533 in combination with MMF, CS, and Tac (standard exposure) in de novo renal transplant patients over the treatment and follow-up period.

Part 2: CNI-free Proof-of-Concept
To assess the potential for CFZ533 to act as the primary immunosuppressant in a CNI-free regimen with MMF in de novo renal transplant patients as assessed by tBPAR at Month 3 posttransplantation.

Secondary:
Part 1: PK, PD and Safety
To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells).
To quantify the change from baseline and recovery of peripheral blood total soluble CD40 and total soluble CD154.
To evaluate the immunogenicity of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies.

Part 2: CNI-free Proof-of-Concept
To assess the safety and tolerability of CFZ533 administered chronically in combination with MMF and CS up to 3 months against a control.
To assess the pharmacokinetics of multiple IV doses of CFZ533 during the 12-month treatment period.
To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells) during the treatment period following multiple IV doses of CFZ533.
To compare renal function in CFZ533 treatment arms to control at Month 3

post-transplantation as assessed by:
Estimated GFR using MDRD
Proportion of patients with eGFR <60 mL/min/1.73m2
Proportion of patients with negative eGFR slope
To evaluate the immunogenicity of multiple IV doses of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies
To quantify the change from baseline and recovery of peripheral blood total soluble CD40 during the treatment period following multiple IV doses of CFZ533.

Study design

A randomized, two-part, 6- or 12-month, sequential, adaptive, controlled, open-label, multicenter, clinical proof-of-concept study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 + MMF + CS, with standard exposure (Part 1) or no tacrolimus (Part 2), for initial and maintenance prophylaxis of organ rejection in adult de novo renal transplant recipients as compared to standard of care.

Part 1 (PK, PD and Safety):
For Arm 1, 6 patients total will be enrolled to receive IV induction (Day 1) and SC administration on Days 15, 29, 43 and 71 of 3 mg/kg CFZ533 with standard-exposure tacrolimus (whole blood trough concentration 4-11 ng/mL), MMF and CS.
Following enrollment of Arm 1, if the interim review of PK/PD data confirms predicted exposure and satisfactory tolerability, Part 2 will initiate enrollment.
All patients enrolled into Part 1 will remain on SoC until Month 6 (EOS).
If the true treatment biopsy-proven acute rejection rate (tBPAR) in Part 1 exceeds 20% (with high probability (>90%) at any time point within three months post-transplant, the treatment arm will be discontinued and hence the study will be terminated.

Part 2 (CNI-free PoC):
Following 2:1 randomization, 45 patients will be enrolled in Arms 2A and 2B in a parallel manner. Arm 2A will receive multiple intravenous CFZ533 10 mg/kg doses with basiliximab induction, MMF and CS; Arm 2B (control) will receive standard-exposure tacrolimus (whole blood trough concentration 4-11 ng/mL) with basiliximab induction, MMF and CS.
Primary endpoints and PoC determination will occur via interim analysis after the Month 3 visit.

The stopping rule described for Part 1 will be in effect in Part 2.

Intervention

Part 1

Arm 1, n=6: CFZ533 at 3.0 mg/kg SC (5 doses; first dose is IV, SC on Days 15, 29, 43 and 71) + tacrolimus (4-11 ng/mL) + MMF 1.0 g BID + CS

Part 2
Arm 2A, n=30: Basiliximab 20 mg (Days 0, 4) + CFZ533 at 10 mg/kg IV (17 doses) + MMF 1.0 g BID + CS
Arm 2B Control/Standard of Care, n=15: Basiliximab 20 mg (Days 0, 4) + tacrolimus (4-11 ng/mL) + MMF 1.0 g BID + CS

Study burden and risks

Study duration: 1 year, 23 visits of 2 hours
Bloodpressure, pulse, bodytemperature 16x
measurement weight 15x and length 1x
Physical examination 4x
Blood and urine tests at each visit (except Day 10)
Pregnancy test every six months
Kidney biopsy if medically necessary
ECG every six months
TB test
Optional tests: pharmacogenetic research.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Written informed consent must be obtained before any assessment is performed.
• Recipients of a kidney transplant from a heartbeating deceased, living unrelated or nonhuman leukocyte antigen (HLA) identical living related donor.
• Recipients of a kidney with a cold ischemia time (CIT) < 30 hours.;See protocol for more details and other inclusion criteria.

Exclusion criteria

• Recipients of an organ from a nonheart beating donor.
• ABO incompatible or complement dependent lymphocytotoxic (CDC) crossmatch positive transplant.
• Subjects receiving a second kidney allograft, unless the first allograft was lost due to surgical complication.
• Subjects at high immunological risk for rejection
• Subjects at risk for tuberculosis (TB)
• Subject with severe systemic infections, current or within the two weeks prior to randomization/enrollment.
• Any additional contraindication to the use of tacrolimus or mycophenolate mofetil according to the
national labeling information of these products (see local product label).;See protocol for more details and other exclusion criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-08-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	25-11-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2016
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	30-10-2017
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	EUCTR2015-000925-36-NL
ClinicalTrials.gov	NCT02217410
CCMO	NL54586.078.15