A 12-month, open-label, multicenter, randomized, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) study of two regimens of anti-CD40 monoclonal antibody, CFZ533 vs. standard of care control, in adult de novo liver transplant recipients with a 12-month additional follow-up and a long-term extension (CONTRAIL I).

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This study will allow the assessment of the ability of CFZ533 to replace calcineurin inhibitors (CNIs) in terms of anti-rejection efficacy, while providing potentially better renal function with an expected similar safety and tolerability profile....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON55608

Source
ToetsingOnline

Brief title
CCFZ533A2202 (CONTRAIL I)

Condition

- Hepatic and hepatobiliary disorders
- Mental impairment disorders
- Renal disorders (excl nephropathies)

Synonym
Liver transplantation

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, liver transplantation

Outcome measures

Primary outcome

Evaluate the rate of composite efficacy failure (Biopsy Proven Acute Rejection

(BPAR), graft loss (GL) or death) with CFZ533 600 mg and 300 mg regimens

compared to tacrolimus (TAC) Control at Month 12 post-transplantation.

Secondary outcome

To evaluate the renal function (estimated Glomerular Filtration Rate (eGFR) by

MDRD-4 formula) with CFZ533 600 mg and 300 mg regimens compared to TAC Control

at Month 12 post-transplantation.

To evaluate the composite of BPAR, Death, Graft Loss and Loss to Follow-up with

CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 and Month

24 post-transplantation.

To evaluate whether CFZ533 600 mg or 300 mg regimens have lower incidence rates

over 12 months and 24 months post-transplantation compared to the control arm for the following events:

- BPAR
- Treated Biopsy Proven Acute Rejection (tBPAR)
- Acute Rejection (AR)
- Treated Acute rejection (tAR)
- Antibody mediated (humoral) rejection
- Graft Loss (GL)
- Death.

To evaluate eGFR and change in eGFR up to Month 24 post-transplantation.

To assess the safety and tolerability of CFZ533 regimens compared to control to Month 12 and Month 24.

To assess the pharmacokinetics of multiple doses of CFZ533 over the 12-month and 24-month treatment and explore the dose-exposure relationship.

To assess the levels of peripheral soluble CD40 (sCD40) at baseline, over the 12-month and 24-month treatment period (to inform target biology, target engagement).

To evaluate the immunogenicity of CFZ533 by analysis of anti-CFZ533 antibodies (over the 12-month and 24-month treatment period).

Study description

Background summary

The purpose of the study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of two calcineurin inhibitor

(CNI)-free regimens of CFZ533, compared to standard of care control, in adult de novo liver transplant recipients.

Study objective

This study will allow the assessment of the ability of CFZ533 to replace calcineurin inhibitors (CNIs) in terms of anti-rejection efficacy, while providing potentially better renal function with an expected similar safety and tolerability profile.
The study results will be used to inform the CFZ533 dose and regimen selection for a pivotal Phase III trial in de novo liver transplant population.

Study design

Study CFZ533A2202 is a randomized, 12-month, active-controlled, open-label, multi-center, dose range finding study to evaluate the efficacy, safety, tolerability, PK and PD of two CFZ533 regimens with a 12-month additional follow-up and a long-term extension in adult de novo liver transplant recipients.

Intervention

- Arm 1 - TAC Control: Tacrolimus + MMF + CS (n=32).
- Arm 2 - CFZ533 600 mg regimen: 30 mg/kg IV (Day 8±1), 15 mg/kg IV (Day 15), then CFZ533 SC 600 mg every 2 weeks from Day 29 to End of Study (EOS) + MMF + CS (n=48).
- Arm 3 - CFZ533 300 mg regimen: 30 mg/kg IV (Day 8±1), and then CFZ533 300 mg every 2 weeks SC from Day 29 to EOS + MMF + CS (n=48).
- For Arm 2 and 3, use of vials from Day 29 to Month 12, and then switch to pre-filed syringes once available.

Study burden and risks

Duration: 2 years, 20-53 hospital visits, 0-28 in-home visits.
Blood pressure, pulse, temperature: 16x
Blood and urine tests: on every (hospital) visit
Pregnancy test: monthly
Liver biopsy: optional at Baseline and M12, and if medically required
ECG: 4-5x
Optional Neurocognitive Tests: 5x

Contacts

Public

Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Screening period up to liver transplantation:
-Male or female subjects between 18 to 70 years of age.
-Recipients of a primary liver transplant from a deceased donor.
-Up to date vaccination as per local immunization schedules.
-Recipients tested negative for HIV.
-MELD score <=30 (based on laboratory values, using the United Network for Organ Sharing (UNOS) MELD calculator: MELD calculator: https://unos.org/resources/allocation-calculators/).
-Transplantation to occur within defined screening period following informed consent signature.
At randomization:
-Recipients with no active HCV and HBV replication. Recipients with HCV antibody positive should have no detectable HCV-RNA. Recipients with Hepatitis B infection should have no detectable HBV DNA. Cases of spontaneous HCV clearance should be discussed with sponsor.
-Allograft is functioning at an acceptable level by the time of randomization as defined by AST, ALT, and Alkaline Phosphatase levels <= 5 times ULN and Total

Bilirubin <= 2 times ULN.
-Renal function (eGFR, MDRD-4 formula) >= 30 mL/min/1.73 m2 based on most recent post-transplant value prior to randomization.
-Recipients who have been initiated on an immunosuppressive regimen that contains TAC, mycophenolate mofetil (MMF) and corticosteroids (CS) as per protocol.

Exclusion criteria

Screening period up to liver transplantation:
-Recipients of multiple solid organ or islet cell transplants, or recipients that have previously received a tissue transplant, or a combined liver-kidney transplant.
-Recipients of a liver from a donor after cardiac death (DCD), from a living donor, or of a split liver.
-Recipient who tests negative for Epstein Barr virus (EBV).
-Recipients receiving an ABO incompatible allograft.
-History of malignancy of any organ system (except hepatocellular carcinoma (HCC) or localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
-Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule <= 5 cm, 2-3 nodules all <= 3 cm, without evidence of metastatic disease or vascular invasion) at the time of transplantation.
-Recipients transplanted for acute liver failure (does not apply to acute on chronic liver failure).
-Any use of antibody induction therapy, or use of any immunosuppressive medications (or other medications prohibited by the protocol)
-Patients who have received a live vaccine within four weeks prior to transplantation.
-Recipients with donors positive for HIV.
-Recipients with donors positive for HBsAg.
-Recipients who are HCV antibody-positive without documented sustained viral response (SVR) at 12 weeks after finishing anti HCV treatment (e.g. direct-acting antivirals).
-Recipients with HCV RNA-positive donors.
At randomization:
-Any post-transplant history of thrombosis, occlusion or stent placement in any hepatic arteries, hepatic veins, portal vein or inferior vena cava at any time during the run-in period prior to randomization.
-Recipients with an absolute neutrophil count of < 1,000/mm^3 or white blood cell count of < 2,000/mm^3.
-Recipients with clinically significant systemic infection requiring use of intravenous (IV) antibiotics.
-Evidence of active tuberculosis (TB) infection (after anti-TB treatment,

patients with history of latent TB may become eligible according to national guidelines).
-Recipients who are on renal replacement therapy at randomization.
-Any episode of acute rejection or suspected rejection prior to randomization.
-HCC participants whose explanted liver graft pathology report shows i) pTNM stage beyond T2N0M0, ii) presence of mixed carcinoma, iii) microvascular invasion despite pTNM stage.
-Participants with body weight < 30 kg or > 180 kg

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:	Recruitment stopped
Start date (anticipated):	19-02-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	(nog) niet van toepassing
Generic name:	iscalimab

Ethics review

Approved WMO Date:	28-05-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2019
Application type:	First submission
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:	27-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-12-2019
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:	19-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2020
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:	16-07-2020
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:	19-01-2021
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:	31-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2023
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	EUCTR2018-001836-24-NL
ClinicalTrials.gov	NCT03781414
CCMO	NL68970.078.19