A Multicentre, Open-Label, Single Ascending Dose, Dose-Ranging, Phase I/IIa Study to Evaluate the Safety and Tolerability of an Autologous Antigen-Specific Chimeric Antigen Receptor T Regulatory Cell Therapy (TX200-TR101) in Living Donor Renal Transplant Recipients.

Published: 12-11-2019
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This study has been transitioned to CTIS with ID 2024-512579-11-00 check the CTIS register for the current data. Primary:- To evaluate the short-term safety and tolerability of TX200-TR101 from the day of TX200 TR101 infusion within 28 days post...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON56213

Source
ToetsingOnline

Brief title
A phase 1/2a study of TX200-TR101 in renal transplant recipients

Condition

- Immune disorders NEC
- Nephropathies

Synonym
Allograft rejection, Renal transplant rejection

Research involving
Human

Sponsors and support

Primary sponsor: Sangamo Therapeutics France SAS
Source(s) of monetary or material Support: Sangamo Therapeutics France SAS

Intervention

Keyword: End Stage Renal Disease, Immunosuppression, Kidney transplant, TX200-TR101

Outcome measures

Primary outcome

Primary:

- Incidence and grade of TEAEs, including SAEs, within 28 days post TX200 TR101

infusion.

Secondary outcome

Key Secondary: Clinical

From the day of TX200-TR101 infusion through to Week 84:

- Incidence of BCAR according to the Banff criteria.

- Time to first BCAR episode.

- Type and severity of any BCAR episodes according to the Banff criteria.

From the day of TX200-TR101 infusion through to Week 84:

- Incidence and grade of TEAEs, including SAEs.

- Incidence of opportunistic infections, specifically BKV, EBV and CMV

reactivation.

- Incidence of neoplasia.

- Proportion of subjects who are receiving tacrolimus monotherapy at Week 84.

- Cumulative dose of immunosuppression, including but not limited to MPA/MMF and tacrolimus through to Week 84.

Key Secondary: Biomarkers

- Presence of CD4 RNA transcript positive cells that are also positive for HLA-A2 CAR RNA transcripts in the renal transplant biopsy at Week 16.

Other Secondary: Clinical

From the day of TX200-TR101 infusion through to Week 84:

- Incidence and severity of chronic graft dysfunction, as measured by eGFR.

- Incidence and severity of chronic graft dysfunction, as measured by the Banff criteria for chronic rejection including the Banff lesion score i-IFTA.

- Incidence of graft loss due to rejection.

- Incidence and (semi-quantitative) intensity of de novo DSA.

Exploratory: Clinical

- Changes from baseline in laboratory parameters, 12-lead ECG and vital signs from the day of TX200-TR101 infusion through to Week 84.

- Incidence of hypertension, dyslipidaemia and new onset diabetes at Week 60 and Week 84 after transplantation.

- Absolute value and change from baseline in SF 36v2® through to Week 84.

Exploratory: Biomarkers

- Proportion of CD4 RNA transcript positive cells that are also positive for HLA-A2 CAR RNA transcripts in the renal transplant biopsy at Week 16, Week 36 and Week 60 (if available).

- Proportion of other RNA transcript positive and negative cells in the renal transplant biopsy at Week 16, Week 36 and Week 60 (if available).

- Levels and changes from baseline in biomarkers in blood and in urine relating to the presence of HLA-A2 CAR Tregs from the day of TX200 TR101 infusion through to Week 84

- Changes from baseline in donor/recipient MLR assays from the day of TX200 TR101 infusion through to Week 60.

- Transcriptomic and proteomic status of cells obtained from the renal biopsies at Day 0, Week 16, Week 36 and Week 60.

- Transcriptomic and proteomic status of cells in blood samples at 1 day before infusion, at 6 and 24 hours post infusion, at Week 14, Week 16, Week 36 and Week 60 (if available).

- 25-hydroxyvitamin D levels in blood samples at screening, and leukapheresis.

Study description

Background summary

Solid organ transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). Despite improvements in short-term outcome, long-term outcome is suboptimal due to the increased morbidity and mortality associated with the toxicity of immunosuppressive regimens and chronic rejection. In the setting of organ transplantation, the requirement for immunosuppressive treatments is lifelong, requiring strict compliance from the patients.

Therapy begins at the time of transplant using induction therapy with high dose intravenous corticosteroids and biological therapies that suppress T cell function or cause T cell depletion. These biologics are potent and only used for specific total doses and in the short time period post operatively. Long-term suppression of the immune response requires a combination of agents taken orally. These typically consist of corticosteroids, a calcineurin inhibitor such as tacrolimus, and an anti metabolite, often mycophenolic acid. These agents are specific to mitigating T cell responses against the allograft.

Conditioning the immune response of solid organ transplant recipients towards allograft acceptance using cell-based therapies is clinically promising and has recently become technically feasible. In early-phase poly-T regulatory cell (Treg) trials in humans T regulatory cell (Treg) appeared to be safe and tolerated over a range of doses. Phase 2 trials have recently commenced and aim to assess the therapeutic potential of these cellular therapies.

With the exception of ABO blood type compatibility, donor/recipient mismatch in HLA antigens such as HLA A*02 is the main contributor for transplant incompatibility and ultimately immune-mediated allograft rejection. TX200-TR101 is a genetically modified cell therapy product. It consists of ex vivo expanded autologous Tregs collected from an HLA-A*02 negative organ recipient prior to transplant, which are genetically modified to express a CAR specific to the donor HLA A*02 at their surface membrane. The aim of this therapeutic approach is the induction of tolerance to the transplanted organ and gradual withdrawal of long-term pharmacological immunosuppression.

Study objective

This study has been transitioned to CTIS with ID 2024-512579-11-00 check the CTIS register for the current data.

Primary:
- To evaluate the short-term safety and tolerability of TX200-TR101 from the day of TX200 TR101 infusion within 28 days post TX200 TR101 infusion.

Key Secondary: Clinical
- To evaluate the effect of TX200 TR101 on acute graft-related outcomes from the day of TX200 TR101 infusion through to Week 84 in terms of BCAR (including type, severity and timing).
- To evaluate the effect of TX200 TR101 on long term safety outcomes from the day of TX200 TR101 infusion through to Week 84 in terms of TEAEs.
- To evaluate the reduction of immunosuppression over time through to Week 84.

Key Secondary: Biomarkers
- To evaluate TX200-TR101 localisation in the graft at Week 16.

Other Secondary: Clinical

- To evaluate the effect of TX200 TR101 on chronic graft related outcomes from the day of TX200-TR101 infusion through to Week 84.

Exploratory: Clinical
- To evaluate the effect of TX200 TR101 on other long-term safety outcomes from the day of TX200-TR101 infusion through to Week 60.
- To evaluate the effect of study treatments on hypertension, hyperlipidaemia and new onset diabetes at Week 52 and Week 60 after transplantation.
- To evaluate quality of life over time through to Week 60.

Exploratory: Biomarkers
- To evaluate TX200-TR101 localisation and its potential impact in the graft at Week 16, Week 36 and Week 60 (if available).
- To characterise the pharmacodynamics of TX200 TR101 from the day of TX200 TR101 infusion through to Week 84, as measured by a panel of biomarkers.
- To explore transcriptomic and proteomic status of cells in the graft and blood via single-cell next generation sequencing.
- To explore 25-hydroxyvitamin D status and its potential influence on Treg cell number and function, and on other immune cells.

Study design

See section 3 in the protocol (page 39-53)

This is a first-in-human, Phase I/IIa, multicentre, open-label, single ascending dose, dose ranging study with a control cohort. The primary objective is to evaluate the short-term safety and tolerability of TX200 TR101 when given as a single ascending dose to HLA-A*02 mismatched living donor renal transplant recipients (HLA A*02 negative recipient and HLA-A*02 positive donor).

All transplant recipients will undergo a screening period to confirm the criteria for participation in the study. Subjects to be administered TX200 TR101 will undergo leukapheresis prior to transplantation. Leukapheresis is not required for control subjects. All transplant recipients will undergo pre-transplant baseline assessments on the day before transplant surgery (Day -1) and will undergo transplant surgery on Day 0. Subjects to be administered TX200 TR101 will receive a single intravenous infusion of TX200-TR101 at Week 12 (±10 days) post-transplant surgery. All transplant recipients (including control subjects) will be followed for 84 weeks post-transplant. The end of this clinical trial is defined as the day when the last subject has completed his/her last visit.

The immunosuppressive regimen will start on the day of transplant surgery. The immunosupppressive regimen will consist of ATG induction, together with intravenous corticosteroids and maintenance with progressive reduction of oral corticosteroids, MPA/MMF and tacrolimus. Discontinuation of the MPA/MMF dose will be possible for subjects administered TX200-TR101, leading ultimately to

tacrolimus monotherapy, depending on the investigator*s decision. Investigators are required at all times to use clinical judgement when considering the immunosuppressive regimen and act in the subject*s best interest to preserve allograft function.

Subjects in the control cohort will undergo transplantation and will receive the same background immunosuppressive agents as the transplant recipients to be administered TX200-TR101, although the dosage of some of the agents will differ.

The duration of study participation will be up to 112 weeks for transplant recipients to be administered TX200-TR101 and up to 88 weeks for control transplant recipients. The duration of study participation for transplant donors will up to 4 weeks (for screening assessments and collection of blood samples for biomarker analysis). The duration and manner of the follow-up of transplant donors should be carried out according to the local institution guidelines. Transplant recipients (including control participants) will be asked if they will participate in an additional, optional long term follow-up study (with separate protocol).

Intervention

See section 7.1 in the protocol (page 71-75).

The investigational medicine (TX200 TR101) is an autologous gene therapy medicinal product composed of Treg (CD4+/CD45RA+/CD25+/CD127low/neg) that have been ex vivo expanded and transduced with a lentiviral vector encoding for a CAR to recognise HLA A*02. The CAR is composed of a ScFv from a humanised antibody that recognises HLA-A*02 molecules, coupled to a transmembrane domain and signalling modules. The composition of the drug product includes purified HLA-A2 CAR Tregs and the components of the cryopreservation medium (CryoStor® CS10) as excipients.

Following TX200 TR101 manufacture, the product will be cryopreserved at a temperature of <= -140°C. The drug product will be provided to the investigational sites in 2 mL sealed vials. Each vial will contain a cell suspension of TX200 TR101 at a fixed cell concentration. The total volume in each vial and the total number of vials for each dose will depend on the dose cohort the transduction efficiency which would give the total number of transduced viable CAR Tregs.

The following premedication will be administered prior to infusion of TX200 TR101:
- Single prophylactic dose of low-molecular-weight heparin, dose adjusted to renal function and body weight as per local policy, to prevent potential thromboembolic complications, if not contraindicated, on the morning of the day of infusion.
- Paracetamol 1 g orally or intravenously to for symptomatic relief of

potential allergic reactions, 30-60 minutes prior to infusion.
- Dimethindene (Fenistil® or similar anti-histamine) 4 mg intravenously to prevent allergic/anaphylactic reactions associated with Treg infusion, 30-60 minutes prior to infusion.
Administration of paracetamol and dimethindene can be repeated every 6 hours if needed.

TX200 TR101 will be infused slowly under the supervision of the study investigator, by trained study staff via a large bore (>=18G) peripheral intravenous cannula in accordance with the infusion rates described in the Cell Therapy Manual. The infusion should be completed as soon as possible following the start of thawing TX200-TR101, please refer to the Cell Therapy Manual for further details.

Study burden and risks

Transplant recipients to be administered TX200-TR101: an up to 112 week participation with approx. 31 study visits. Additional blood draws and biopsies are performed. A leukapheresis procedure will be required. These participants will be exposed to the investigational medicine and subsequent risks. However, these participants can potentially benefit from the study medicine (when compared to standard post-transplant care). Moreover, they will contribute to increased knowledge about solid organ transplants and this may be of future benefit to those who will undergo this procedure and receive post-transplant care.

Control transplant recipients: an up to 64 week participation with approx. 22 study visits. Additional blood draws are done and there are (optional extra) biopsies performed. Additional assessments and monitoring will take place for control participants. They will also get the option for a (separate) long-term follow-up study. Moreover, they will contribute to increased knowledge about solid organ transplants and this may be of future benefit to those who will undergo this procedure and receive post-transplant care.

Live transplant donors: a up to 4 week participation with 1 or 2 study visits. The only invasive procedure is the collection of blood. Donors will not personally benefit from the study. However, they will contribute to increased knowledge about solid organ transplants and this may be of future benefit to those who will undergo this procedure and receive post-transplant care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria (All Transplant Recipients)
1. Willing and able to provide written informed consent (IC) in accordance with local regulations and governing Independent Ethics Committee (IEC)/Institutional Review Board (IRB) requirements prior to any procedure or evaluation performed specifically for the sole purpose of the study.
2. Male or female aged between 18 and 70 (inclusive) years.
3. Have diagnosis of ESRD and currently waiting for a new kidney from an identified live donor.
4. Subjects who will be single organ recipients (kidney).
5. Normal or non-clinically significant abnormality in the electrocardiogram (ECG), at investigator*s discretion.
6. Women who are of childbearing potential must have a negative serum pregnancy test at screening and before transplantation.
7. Able and willing to use a highly effective method of contraception from the signing of the informed consent through the last study visit, for male and female subjects with reproductive potential.

Additional Inclusion Criteria (Transplant Recipients to be Administered TX200

TR101 Only)
1. HLA-A*02 negative typing (the kidney graft needs to be HLA A*02 positive).
2. HLA-A*69 negative typing.
3. Adequate venous access for leukapheresis, and no other contraindications for leukapheresis.
4. Subjects that have a transplant planned or scheduled for at least 10 weeks after the time of enrolment.

Inclusion Criteria (All Transplant Donors)
1. Willing and able to provide written IC in accordance with local regulations and governing IEC/IRB requirements prior to any procedure or evaluation performed specifically for the sole purpose of the study.
2. Aged at least 18 years on the day of signing the IC form.
3. ABO blood type compatible with the organ recipient.
4. Negative serology for HIV, HBV, HCV and syphilis.
5. Willing to provide personal and medical/biological data and samples for the study analysis.

Additional Inclusion Criterion (Transplant Donors for Transplant Recipients to be Administered TX200 TR101 Only)
1. HLA-A*02 positive typing.

Exclusion criteria

Exclusion Criteria (All Transplant Recipients) 1. HLA identical to the prospective organ donor. 2. Subjects with prior organ transplant. 3. Known hypersensitivity to study medication ingredients or a significant allergic reaction to any drug as determined by the investigator, such as anaphylaxis requiring hospitalisation. 4. Known hypersensitivity or contraindications for anti-thymocyte globulin (ATG), tacrolimus or mycophenolic acid (MPA)/ mycophenolate mofetil (MMF). 5. Positive serology for human immunodeficiency virus (HIV) or syphilis. 6. Evidence of active or occult hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. 7. Subjects who are Epstein-Barr Virus (EBV) seronegative. 8. Positive flow cytometric crossmatch using donor lymphocytes (T and B cells) and recipient serum. 9. Subjects with panel-reactive antibody (PRA) >20% within 6 months prior to enrolment. 10. Subjects with current, recent or historical donor-specific antibodies. 11. Previous treatment with any desensitisation procedure (with or without intravenous immunoglobulin) 12. Subjects with underlying renal disease with a high risk of disease reoccurrence in the transplanted kidney including primary focal segmental glomerulosclerosis, C3 glomerulopathy, types I or II membranoproliferative glomerulonephritis or haemolytic-uraemic syndrome (HUS), including a typical HUS. If the subject has ESRD of unknown aetiology and/or has no histologically confirmed diagnosis the subject may be enrolled into the study if there are no clinical, laboratory, histological or genetic features

suggestive of a diagnosis of primary focal segmental glomerulosclerosis, types I or II membranoproliferative glomerulonephritis, C3 glomerulopathy, or HUS, including atypical HUS, as deemed by the investigator. 13. Concomitant clinically active local or systemic infection. 14. Use of any experimental medicinal product within 3 months or 5 half-lives prior to the screening visit, whichever is longer, and agreement to not take any experimental medicinal product throughout the trial. 15. Subjects who are currently receiving systemic immunosuppressive agents (e.g., methotrexate, infliximab, adalimumab, corticosteroids) for other indications such as autoimmune diseases, or subjects with comorbidities for which treatment with such agents are likely during the study, with the following exception: • Subjects who are receiving or may require short-term and/or low dose (e.g., prednisone or prednisone equivalent < 5 mg daily) or methotrexate (e.g. 15 mg weekly) courses of corticosteroids are not precluded from enrolment, at the discretion of the investigator in consultation with the Sponsor*s Medical Monitor. 16. Clinical evidence of significant unstable or poorly controlled acute or chronic diseases (i.e., cardiovascular, pulmonary, haematologic, gastrointestinal, hepatic, neurological, or infectious diseases) or laboratory abnormality (except ESRD) which, in the opinion of the investigator, could confound the results of the study or put the subject at undue risk. • Subjects who, at the discretion of the investigator, are deemed at high risk of a renal thrombotic event. 17. Subjects with current or previous history of clinically relevant central nervous system pathology (including but not limited to seizures within the last 5 years, stroke within the last 5 years, severe brain injury, cerebellar disease or CNS vasculitis). 18. Current or previous history within the last 5 years of malignancy, with the following exceptions: • Subjects with any previous history of haematological malignancy are precluded from enrolment. • Subjects who have had non-melanoma skin cancer or cervical carcinoma in situ that has been successfully treated with no evidence of recurrence are not precluded from enrolment. 19. Subjects whose life expectancy is severely limited by disease state other than renal disease. 20. Subjects with a history of substance abuse (drug or alcohol) within the past 2 years or that is considered not compatible with adequate study follow-up, or psychiatric disorder or other condition that is not compatible with adequate study follow-up. 21. Subjects with laboratory values that meet the following criteria are to be excluded (retesting once during the screening period is permitted at the investigator*s discretion): • Haemoglobin < 9 g/dL (or <5.59 mmol/L) • Platelets < 80 x 10^9/L • White blood cells (WBC) < 3 X 10^9/L • Aspartate transaminase (AST) and or alanine transaminase (ALT) >= 3 x upper limit of normal (ULN) • Total bilirubin >= 2 x ULN (except for subjects with Gilbert*s disease) 22. Subjects who will have received a live attenuated vaccine (LAV) within 30 days prior to their transplantation surgery. 23. Subjects who are currently pregnant, planning pregnancy or breast feeding/lactating while enrolled in the study. 24. Any other reason that, in the opinion of the Site Investigator or Medical Monitor, would render the subject unsuitable for participation in the study. This includes, but is not limited to, subjects unable to give their own consent (e.g. those under guardianship, curatorship or

sauvegarde de justice). Investigators, employees of the investigative site, and their immediate families. Immediate family is defined as the Investigator's or employees* current spouses, parents, natural or legally adopted children (including stepchildren), grandparents, or grandchildren. Sponsor employees. Subjects institutionalised because of legal or regulatory order, inmates of psychiatric wards, prison or state institutions. Wards of court. Exclusion Criteria (All Transplant Donors) 1. Genetically identical to the prospective organ recipient. 2. Exposure to investigational agents at the time of kidney donation or within 28 days or 5 half-lives whichever is longer, prior to the donation. 3. Any form of substance abuse considered not compatible with adequate study follow up, psychiatric disorder or other condition that in the opinion of investigator may compromise study participation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-09-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	12-11-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-04-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	01-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2022
Application type:	Amendment
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Approved WMO Date:	31-03-2022
Application type:	Amendment
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2023
Application type:	Amendment
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Approved WMO Date:	06-03-2023
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	Haag)
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Application type:	Amendment
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Approved WMO Date:	09-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EU-CTR	CTIS2024-512579-11-00
EudraCT	EUCTR2019-001730-34-NL
CCMO	NL70193.000.19