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Primary Objectives 1. To evaluate the efficacy of clazakizumab in preventing all-cause composite allograft loss (including death) due to CABMR.2. To evaluate the efficacy of clazakizumab in slowing/preventing the progressive loss of kidney function…

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

Summary

ID

NL-OMON54769

Source

ToetsingOnline

Brief title

IMAGINE
3940/0006

Condition

- Other condition

Synonym

kidney rejection treatment

Health condition

Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients

Research involving

Human

Sponsors and support

Primary sponsor :	-
Source(s) of monetary or material Support :	Transfer from Vitaeris Inc to CSL Behring LLC per 15Aug2020

Intervention

Keyword :	Clazakizumab, Double blind/placebo, Kidney Transplant Rejection, Phase 3

Outcome measures

Primary outcome

1. To evaluate the efficacy of clazakizumab in preventing all-cause composite

allograft loss (including death) or irreversible loss of allograft function,

due to CABMR.

2. To evaluate the efficacy of clazakizumab in slowing / preventing the

progressive loss of kidney function (as measured by eGFR using the Modification

of Diet in Renal Disease 4 [MDRD4] equation [Interim Analysis #2 {IA #2}]).

3. To evaluate the safety of clazakizumab.

Secondary outcome

1. To evaluate the efficacy of clazakizumab in preventing all-cause allograft

loss

(including death) due to CABMR.

2. To evaluate the effects of clazakizumab on loss of allograft function

(defined as a

40% decline in eGFR from Baseline that is sustained for at least 60 days).

3. To evaluate the effects of clazakizumab on death-censored allograft loss.

4. To evaluate the effects of clazakizumab on albuminuria.

5. To evaluate the effects of clazakizumab on DSA titers and mean fluorescence

intensity (MFI) scores.

6. To evaluate the effects of clazakizumab on the histology of kidney biopsies

according to the Banff 2015 lesion grading scores.

7. To evaluate the effects of clazakizumab on incidence of acute rejection

episodes

(TCMR and ABMR).

8. To evaluate the effects of clazakizumab on overall subject survival.

9. To evaluate the PK of clazakizumab following subcutaneous (SC) injection in

kidney

transplant recipients with CABMR (for those subjects in the Pharmacokinetic

[PK] /

Pharmacodynamic [PD] Substudy only).

10. To evaluate the immunogenicity of clazakizumab in kidney transplant

recipients with

CABMR.

Study description

Background summary

Clazakizumab is being developed by the sponsor (Vitaeris Inc.) for the treatment of Chronic Active Antibody-Mediated Rejection in Kindney Transplant recipients. The clazakizumab development program includes a comprehensive nonclinical development program and clinical studies (conducted by previous sponsors of the drug) in healthy subjects and in subjects with rheumatoid arthritis, psoriatic arthritis, Crohn*s disease,graft-versus-host disease, and oncology. To date, no studies with clazakizumab have been completed in kidney transplant recipients, although supporting safety data are available from the previous clinical studies. Clazakizumab is an antibody (a protein made in yeasts) that blocks another protein called interleukin 6 (IL-6) which is present in the blood. IL-6 is important in inflammation and may be responsible for the development of antibody-mediated rejection in patients who have received a kidney transplant. To date, over 1,000 people (healthy volunteers, patients with rheumatoid arthritis, psoriatic arthritis, Crohn*s disease, graft-versus-host disease, advanced cancer, and your disease) have taken this investigational drug in clinical studies.

Study objective

Primary Objectives
1. To evaluate the efficacy of clazakizumab in preventing all-cause composite allograft loss (including death) due to CABMR.
2. To evaluate the efficacy of clazakizumab in slowing/preventing the progressive loss of kidney function (as measured by eGFR using the Modification of Diet in Renal Disease 4 (MDRD4) equation).
3. To evaluate the safety of clazakizumab.

Secondary Objectives
1.To evaluate the efficacy of clazakizumab in preventing all-cause allograft loss (including death) due to CABMR
2.To evaluate the effects of clazakizumab on loss of allograft function
3.To evaluate the effects of clazakizumab on death-censored allograft loss
4.To evaluate the effects of clazakizumab on albuminuria
5.To evaluate the effects of clazakizumab on DSA titers and mean fluorescence intensity scores
6.To evaluate the effects of clazakizumab on the histology of kidney biopsies according to the Banff 2015 lesion grading scores
7.To evaluate the effects of clazakizumab on incidence of acute rejection episodes (TCMR and ABMR)
8.To evaluate the effects of clazakizumab on overall subject survival
9.To evaluate the PK of clazakizumab following subcutaneous injection in kidney transplant recipients with CABMR (for those subjects in the

Pharmacokinetic/Pharmacodynamic Substudy only)
10.To evaluate the immunogenicity of clazakizumab in kidney transplant recipients with CABMR

Study design

Randomized, double-blind, parallel-group, placebo-controlled, phase 3 multicenter study. Subjects will receive treatment with either 12.5 mg clazakizumab (n = 175) or placebo (n = 175) by SC injection Q4W until permanent discontinuation of Investigational Product (IP), withdrawal from the study, allograft loss, death, or the common treatment end date (CTED) is reached, whichever occurs first). The common treatment end dateCTED is the date when the primary efficacy endpoint (all-cause composite allograft loss) is achieved, ie, the date the prescribed target number of primary composite all-cause allograft loss or irreversible loss of allograft lossfunction events (221) has been reached.

Intervention

Investigational Medicinal Product: clazakizumab single-dose vials (12.5 mg/mL) for SC injection.

Study burden and risks

See the separate document (D2 Risk Benefit Assessment)

Contacts

Public
-

CSL Behring LLC 1020 First Avenue
King of Prussia PA 19406
US
Scientific
-

CSL Behring LLC 1020 First Avenue
King of Prussia PA 19406

US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

1. Age 18-75 years.
2. Living donor/deceased donor kidney transplant recipients >=6 months from time of transplant.
3. Diagnosis of CABMR determined by kidney biopsy and the presence of HLA DSA using single-antigen bead-based assays. For eligibility, kidney biopsy must not be older than 12 months and DSA analysis must be performed no longer than 6 months prior to the start of Screening.
NOTE: • Within 3 months prior to the start of Screening, treatments for ABMR or TCMR, with the exception of steroids*, are not allowed (see Exclusion Criterion 3).
• If treatment for ABMR (including CABMR) or TCMR (other than steroids*) was given between 3 to 12 months of Screening, a repeat kidney biopsy and DSA analysis are required at least 6 weeks after the end of treatment to confirm continuing CABMR and presence of HLA DSA and to determine eligibility.
* A maximum dose of 2g of methylprednisolone intravenously (or dose equivalent of other steroids), followed by a taper to the original maintenance steroid dose is allowed.
The following histopathologic and serologic diagnostic criteria (based on Banff 2015 criteria [Loupy et al, 2017]) must be met for inclusion:
a. Morphologic evidence of chronic tissue injury, as demonstrated by transplant glomerulopathy (TG) (cg) > 0). Biopsies without evidence of chronic tissue injury on light microscopy, but with glomerular basement membrane double contours on electron microscopy (cg1a) are eligible.
b. Evidence of current/recent antibody interaction with vascular

endothelium, including 1 or more of the following:
i. Linear C4d staining in peritubular capillaries or medullary vasa recta (Banff scores C4d2 or C4d3 by immunofluorescence on frozen sections, or C4d > 0 by immunohistochemistry on paraffin sections).
ii. At least moderate microvascular inflammation (glomerulitis score, [g] + peritubular capillaritis score [ptc] >= 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc >= 2 alone is not sufficient and g must be >= 1.
NOTE: The local pathologist's diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study. Biopsies with other histopathologic changes (eg, BKV nephropathy or recurrent glomerulonephritis) may be eligible if concurrent CABMR changes (as detailed above) are present and determined to be the predominant cause of renal dysfunction.
c. Serologic evidence of circulating HLA DSA.
NOTE: The local laboratory DSA results must be reviewed and confirmed by the central HLA reviewer during the screening period.
4. Written informed consent obtained from subject (or legally acceptable representative) before any trial-related procedures.

Exclusion criteria

11.A8 Subject is unable or unwilling to comply with study procedures in the opinion of
the Investigator.
2.A6 Multi-organ transplant recipient (except for simultaneous kidney-pancreas or
previous multiple kidney transplants) or cell transplant (islet, bone marrow, stem
cell) recipient.
3. Treatment for ABMR (including CABMR) or TCMR within 3 months prior to the start of Screening with the exception of steroids.
4. Received T cell depleting agents (eg, alemtuzumab, anti-thymocyte globulin) within 3 months prior to the start of Screening.
5. Treatment with mTOR inhibitors within 4 weeks prior to the start of Screening (see Section 7.6.1).
6.A8 Biopsy indicating predominant cause of renal dysfunction caused by pathology
other than CABMR, within 12 months (± 3 weeks) of Screening.
7.A8 Impaired renal function due to disorders in the transplanted allograft (eg, renal
artery stenosis, significant vascular disease of the donor, hydronephrosis).
8. eGFR < 25 mL/min/1.73 m2 or > 65 mL/min/1.73 m2 (MDRD4).
9.A8 Nephrotic range proteinuria defined as spot urine albumin-to-creatinine

ratio
(UACR) >= 2200 mg/g (>= 248.4 mg/mmol). If spot UACR is above the defined limits, a single repeat test can be performed on a separate day to confirm ineligibility.
10. Pregnant, breastfeeding, or unwillingness to practice adequate contraception (eg,
a highly effective or acceptable method of contraception) during the study and for 5 months after the last dose of IP.
11. History of anaphylaxis or known hypersensitivity to clazakizumab or to any constituent of the drug product.
12.A8 Abnormal liver function tests (LFTs [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or bilirubin > 1.5 x upper limit of normal]) or other significant liver disease. Subjects with an established diagnosis of Gilbert*s
syndrome are allowed.
13.A8 Active tuberculosis (TB) or history of active TB.
14.A8 History of latent TB (eg, positive QuantiFERON-TB test) without history of active TB unless the subject has completed a documented course of prophylactic treatment.
15. History of human immunodeficiency virus (HIV) infection or positive for HIV.
16. Seropositive for hepatitis B surface antigen (HBsAg).
17. Hepatitis C virus (HCV) RNA positive.
18.A8 Known EBV mismatch (at time of transplant): donor seropositive, recipient seronegative. Seroconversion to EBV IgG-positive post-transplant is allowed, if documented.
19.A8 History of gastrointestinal (GI) perforation; diverticular disease defined as
clinically significant diverticulosis (except if disease has been fully excised and
the subject has recovered from surgery) or diverticulitis (except if disease has been fully excised and the subject has recovered from surgery); or inflammatory bowel disease (except fully excised ulcerative colitis and the subject has recovered from surgery).
20.A8 Neutropenia (< 1500/mm3) or thrombocytopenia (< 75,000/mm3).
21. Active infections requiring systemic antimicrobial agents and unresolved prior to
Screening.
22.A8 History of or current invasive fungal infection or other opportunistic infection,
including (but not limited to) the following: a nontuberculous mycobacterial infection, aspergillosis, pneumocystosis, and toxoplasmosis, etc.
23.A8 Active viral infections such as BKV, CMV, or EBV based on plasma polymerase chain reaction (PCR) testing. Active infection is defined as a test result >= lower limit of quantification (LLOQ) (see definition in Table 6).
24. Current or recent (within 3 months) participation in an interventional trial.
25. Administration of a live vaccine within 6 weeks prior to the start of

Screening,
including but not limited to the following:
a. Adenovirus.
b. Measles, mumps, and rubella.
c. Oral polio.
d. Oral typhoid.
e. Rotavirus.
f. Varicella zoster.
g. Yellow fever.
26.A8 History of alcohol or illicit substance (including marijuana) abuse < 5 years
before Screening.
27.A8 Present or previous (within 3 years) malignancy except for basal cell carcinoma,
fully excised squamous cell carcinoma of the skin; other malignancies or those that required significant therapy may require longer duration documented cancerfree
(5 years) such as nonrecurrent cervical carcinoma in-situ or malignancy treated with resection and chemotherapy. These cases should be discussed with the Medical Monitor and Sponsor on a case-by-case basis.
28. The presence of a condition or abnormality (ie, clinically significant endocrine,
autoimmune, metabolic, neurological, psychiatric / psychological, renal, GI, hepatic, and hematological or any other system abnormalities that are uncontrolled with standard treatment) that in the opinion of the Investigator would compromise the safety or life expectancy of the subject or the quality of the data.
29History of intolerance to trimethoprim and / or sulfamethoxazole. This criterion
does not apply if the subject is already taking another suitable Investigatorapproved
alternative therapy for PJP prophylaxis, or if the subject is willing to begin taking a suitable Investigator-approved alternative prophylactic therapy at
least 1 week prior to the Day 1 Baseline Visit (Visit 2).
30. Prior exposure to clazakizumab, TCZ, or other IL-6 / IL-6R blockers.
31. ABO-incompatible transplant recipient.
32. Severe hypogammaglobulinemia (defined as immunoglobulin G [IgG] < 400 mg/dL).
33. Prior (within 2 years prior to the start of Screening) exposure to proteasome
inhibitors (eg, bortezomib).
34.A8 Active infection with coronavirus disease 2019 (COVID-19):
a. Subject not known to have been previously infected with COVID-19 must have a negative PCR test result during the Screening Period as near to the Day 1 Baseline Visit (Visit 2) as possible. If the subject is unwell with symptoms suggestive of COVID-19 but PCR test result is negative, other

causes for symptoms must be ruled out to determine subject eligibility.
Note: If the subject was not previously known to have been infected with COVID-19 and has a positive PCR test result at Screening, criterion 34.A8b must be met.
b. Subject known to have been previously infected with COVID-19 must meet all the following conditions:
i. Must be without symptoms attributable to COVID-19 for at least 1 month prior tothe start of Screening.
ii. Must be re-established on background immunosuppressants for at least 2 weeks prior to the start of Screening.
35.A8 For subjects receiving anti-hypertensive agents (eg, ACEIs or ARBs), the dose
of the agent should be stable for at least 2 months prior to the start of Screening
and not planned to be increased.

Study design

Design

Study phase :	3
Study type :	Interventional
Intervention model :	Parallel
Allocation :	Randomized controlled trial
Masking :	Double blinded (masking used)
Control :	Placebo
Primary purpose :	Treatment

Recruitment

NL

Recruitment status :	Recruiting
Start date (anticipated) :	15-07-2021
Enrollment :	30
Type :	Actual

Medical products/devices used

Product type :	Medicine

Brand name :	clazakizumab
Generic name :	clazakizumab

Ethics review

Approved WMO Date :	27-03-2019
Application type :	First submission
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	21-06-2019
Application type :	First submission
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	23-03-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	11-05-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	22-06-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	23-06-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	09-09-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date :	18-09-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	07-12-2020
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	19-02-2021
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	03-06-2021
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	06-06-2021
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	12-11-2021
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	21-06-2022
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	01-10-2022
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date :	07-10-2022
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	31-10-2022
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	07-11-2022
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	11-06-2023
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	31-08-2023
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	25-10-2023
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date :	09-11-2023
Application type :	Amendment
Review commission :	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2018-003682-34-NL
CCMO	NL68797.056.19