A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON48649

Source
ToetsingOnline

Brief title
CCX168C3G

Condition

- Renal disorders (excl nephropathies)

Synonym
C3 Glomerulopathy

Research involving
Human

Sponsors and support

Primary sponsor: Chemocentryx
Source(s) of monetary or material Support: ChemoCentryx Inc.

Intervention

Keyword: avacopan, C3 Glomerulopathy, C3G

Outcome measures

Primary outcome

The primary efficacy endpoint is the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity.

Secondary outcome

Other efficacy endpoints include:

1. The proportion of patients who have a histologic response, defined as a decrease (improvement) in the C3G Histologic Index for activity of at least 35% from baseline to Week 26;

2. The percent change from baseline in the C3G Histologic Index for disease chronicity over the placebo-controlled 26-week treatment period;

3. The change and percent change from baseline in eGFR over the placebo-controlled 26-week treatment period;

4. The percent change from baseline in UPCR over the placebo-controlled 26-week treatment period;

5. The percent change from baseline in urinary MCP-1:creatinine ratio over the placebo-controlled 26-week treatment period;

6. Change from baseline in EQ-5D-5L (visual analogue scale and index) and SF-36 v2 (domains and component scores) over the placebo-controlled 26-week treatment

period.

Safety endpoints include:

1. Patient incidence of treatment-emergent serious adverse events, adverse

events, and study withdrawals due to adverse events;

2. Change from baseline and shifts from baseline in all safety laboratory

parameters;

3. Change from baseline in vital signs.

Study description

Background summary

C3G is characterized by evidence of alternative complement activation based on C3 deposition in the glomeruli. There are two forms of the disease: dense deposit disease (DDD, formerly called membranoproliferative glomerulonephritis [MPGN] Type II) and C3 glomerulonephritis
(C3GN, formerly called idiopathic MPGN). Genetic mutations leading to defective complement regulation, including reduced-function mutations of complement factor H (CFH), have been described in some of these patients. Patients with C3G often have progressive deterioration in renal function, ultimately leading to end-stage renal disease.

There is no approved treatment for patients with C3G. Immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, and glucocorticoids, as well as biologics such as rituximab have been used with limited success. The anti-C5 antibody eculizumab previously
showed evidence of improvement in some patients with C3G. Eculizumab blocks the formation of C5a and C5b-9 (membrane attack complex) from C5. Evidence from animal models suggest that inhibition of C5a may be more important than inhibition of C5b-9 in C3G, because deletion
of C6 (which is part of the C5b-9 complex) in CFH knockout mice failed to protect the mice from developing symptoms of C3G (Pickering et al, 2006). This provides support for testing drugs that target C5aR, such as avacopan.

Avacopan is an orally administered, selective inhibitor of the complement 5a receptor (C5aR) which is in Phase 3 clinical development for treatment of

patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Phase 2 study data with avacopan in patients with AAV indicate efficacy with 30 mg avacopan given twice daily based on improvement in disease activity (Birmingham Vasculitis Activity Score), a significant antiproteinuric effect, and improvement in quality of life among other improved disease parameters (Jayne et al, 2017). This treatment effect was observed in subjects receiving avacopan plus cyclophosphamide or rituximab, but with no oral glucocorticoids.

One patient with treatment refractory C3GN, one of the subtypes of C3G, has been treated successfully with 30 mg avacopan twice daily since September 2015 under a *Special Needs* program in the UK. This patient had progressive decline in renal function despite previous
treatment with immunosuppressants, rituximab, and glucocorticoids, as well as a kidney transplant.

Study objective

The primary objective is to evaluate the efficacy of avacopan compared to placebo based on histologic changes in kidney biopsies taken before and during treatment.

The secondary objectives of this study include evaluation of:
1. The safety of avacopan compared to placebo based on the incidence of adverse events, changes in clinical laboratory measurements, and vital signs;
2. Changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), proteinuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) with avacopan compared to placebo;
3. Health-related quality-of-life changes based on Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L) with avacopan compared to placebo;
4. The pharmacokinetic profile of avacopan in patients with C3G.
Additionally, changes from baseline in markers of alternative complement pathway involvement and other markers of inflammation may be assessed in plasma/serum or urine over the course of the treatment period.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter phase 2 study.

Intervention

The subjects will be randomized 1:1 to receive 30 mg avacopan twice daily or matching placebo for 26 weeks in a double-blind, placebo-controlled manner. The primary efficacy analysis will occur when the last enrolled subject has completed the Week 26 visit. After the 26-week double-blind period, the avacopan group will continue receiving avacopan for another 26 weeks, and the

placebo group subjects will be switched over in a blinded manner to receive 30 mg avacopan twice daily treatment, instead of placebo, for another 26 weeks.

Study burden and risks

Risks: possible side effects of the study drug and study procedures.

Burden:
Daily taking of the study medication.
There are 22 visits during a period of 62 weeks. The following study procedures will be conducted:
Blood draws
Urine samples
The patient needs to complete questionnaires
Physical examination
Vital signs measurement
During 7 visits (including the screening visit) an ECG is made
Pregnancy tests if applicable

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Biopsy-proven C3G, either DDD or C3GN, with or without a renal transplant, and with the following observations upon renal biopsy taken within 12 weeks prior to screening or during screening:
a. >=2-levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q by immunohistochemistry, and
b. evidence of proliferative glomerulonephritis (mesangial hypercellularity of greater than 3 mesangial cells per mesangial area and/or endocapillary hypercellularity defined as an increased number of cells within glomerular capillary lumina, causing luminal narrowing) based on light microscopy, and
c. confirmation of the presence of electron dense deposits in the glomeruli on electron microscopy corresponding with the C3 immunofluorescence positivity;
2. Male or female patients, aged at least 18 years; where approved, adolescents (12-17 year old) may be enrolled; female patients of childbearing potential (i.e., those who have experienced menarche and who is not permanently sterile or postmenopausal, defined as at least 12 consecutive months with no menses without an alternative medical cause) may participate if adequate contraception is used during, and for at least the three months after study completion; Male patients with partners of childbearing potential may be excluded if they plan to father a child during the study; Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient. In addition, a barrier method (i.e., cervical cap, diaphragm or condom) must be used during intercourse between a male patient and a female of child-bearing potential;
3. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; written Assent and Informed Consent must be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age; and
4. Judged to be otherwise fit for the study by the Investigator, based on medical history, physical examination, and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other

abnormal clinical findings that are judged by the Investigator not to be of clinical significance, may be entered into the study. At sites in which adolescents are allowed to be enrolled, the Investigator assures that the adolescent patient is willing and able to ingest the size "0" study drug.

Exclusion criteria

1. Pregnant or nursing;
2. Tubulointerstitial fibrosis appears to be more than 50% based on standard assessment using trichrome staining of the renal biopsy;
3. Use of eculizumab or another anti-C5 antibody within 26 weeks prior to dosing;
4. Secondary C3 disease, e.g., infection-associated disease, or associated with another systemic or autoimmune disease; presence of a monoclonal spike on serum or urine protein electrophoresis or immunofixation assay;
5. Currently on dialysis or likely will require dialysis within 7 days after screening;
6. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
7. Positive HBV, HCV, or HIV viral screening test indicative of acute or chronic infection;
8. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done at screening or within 6 weeks prior to screening; a CT scan or chest X-ray are not mandatory if evidence of tuberculosis was excluded by any of the other methods specified above;
9. Active uncontrolled infection;
10. WBC count less than 3500/mL, or neutrophil count less than 1500/mL, or lymphocyte count less than 500/mL before start of dosing;
11. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin >3 x the upper limit of normal before start of dosing;
12. Currently using a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John*s wort;
13. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or Cremophor) or inability to swallow the capsules;
14. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose; and
15. History or presence of any medical condition (for example: contraindication to local anesthesia required for renal biopsy, or recurring serious infections) or disease which, in the opinion of the Investigator, may place the patient at

unacceptable risk for study participation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2018
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CCX168
Generic name:	avacopan

Ethics review

Approved WMO Date:	16-10-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2018

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-001821-42-NL
CCMO	NL62908.018.17