A phase III, multicenter, randomized, double-blind placebo-controlled study to assess the efficacy and safety of Tocilizumab in subjects with giant cell arteritis.

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Primary Efficacy Objective:• To evaluate the efficacy of tocilizumab (TCZ) compared to placebo, in combination with a26-week prednisone taper regimen, in patients with giant cell arteritis (GCA), as measured by the proportion of patients in...

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

Summary

ID

NL-OMON39663

Source
ToetsingOnline

Brief title
Roche GCA WA28119

Condition

- Immune disorders NEC

Synonym
Giant Cell Arteritis, Temporal Arteritis

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: GCA, giant cell arteritis, temporal arteritis, tocilizumab

Outcome measures

Primary outcome

Efficacy Outcome Measures:

1) Assessment of GCA disease activity based on the presence or absence of signs

and symptoms

2) Assessment of acute phase reactants ESR and CRP

3) Assessment of prednisone dose and duration

Secondary outcome

Safety Outcome Measures:

1) Incidence, nature, and severity of adverse events

2) Laboratory abnormalities including but not limited to neutropenia, liver

function test abnormalities, thrombocytopenia, and lipid level abnormalities

3) Incidence of anti-TCZ antibodies

Pharmacodynamic Outcome Measures:

1) IL-6

2) sIL-6R

3) ESR and CRP

Pharmacokinetic Outcome Measures:

1) TCZ concentration

2) Derived PK parameters as follows:

- AUC*, Cmax, and Cmin at steady state for 162 mg qw and 162 mg q2w for

patients in the PK substudy

- Predose TCZ concentration (Ctrough) for all patients

Patient-Reported Outcome Measures:

1) PGA (VAS)

2) SF-36

3) EQ-5D

4) FACIT-Fatigue

Study description

Background summary

Corticosteroids (CS) are the mainstay of treatment for GCA. Although CS are highly effective at inducing remission of systemic inflammation and preventing acute damage (e.g., blindness), this comes with a high toxicity burden, with 86% of patients suffering CS-related adverse clinical events at 10-year follow-up.
In addition, CS are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare-up of symptoms during reduction or discontinuation of CS.
An effective and safe CS-sparing therapy for patients with new-onset or refractory GCA remains elusive and constitutes a high unmet medical need.

Study objective

Primary Efficacy Objective:
• To evaluate the efficacy of tocilizumab (TCZ) compared to placebo, in combination with a

26-week prednisone taper regimen, in patients with giant cell arteritis (GCA), as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen

Key Secondary Objective
• To evaluate the efficacy of TCZ in combination with a 26-week prednisone taper regimen versus placebo in combination with a 52-week prednisone taper regimen, in patients with GCA, as measured by the proportion of patients in sustained remission at Week 52 following induction and adherence to the protocol-defined prednisone taper regimen

Other secondary objectives:
1) To assess the efficacy of TCZ in combination with a 26-week prednisone taper regimen versus both placebo groups, in patients with GCA
2) To assess the effect on patient*s quality of life of TCZ in combination with a 26-week prednisone taper regimen versus placebo based on the patient-reported outcome (PRO)
3) To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ in combination with a 26-week prednisone taper regimen in patients with GCA

Study design

This is a Phase III, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial in patients with GCA. The primary endpoint, the proportion of patients in sustained remission, will be evaluated at 52 weeks. There will be a 52-week blinded period (Part 1) followed by a 104-week open-label period (Part 2), with a total duration of the study of 156 weeks.

Intervention

A planned total of approximately 250 patients will be enrolled and assigned to one of four arms. Patients will be randomized in a 2:1:1:1 ratio to receive the following treatments:
• Group A: 162 mg of subcutaneous (SC) TCZ every week (qw) + 26-week prednisone taper regimen (n = 100)
• Group B: 162 mg of SC TCZ every other week (q2w) + 26-week prednisone taper regimen (n =50)
• Group C: SC placebo + 26-week prednisone taper regimen (n = 50)
• Group D: SC placebo + 52-week prednisone taper regimen (n = 50)

Study burden and risks

1) Assessments during screening: tuberculosis screening, physical examination, vital signs, weight, height, ECG, thorax X-ray, blood sample, urine sample, GCA assessment.

2) Assessments during part 1 (52 wks, double blind, max. 18 planned visits): physical exam 1x, vital signs all visits, weight 3x, blood sample all visits, questionnaires 6x, urine sample 1x, GCA assessment all visits.

3) Assessments during part 2 (2nd and 3rd year, open label extension/long term follow-up, max 13 planned visits): physical exam 1x, vital signs 6x, weight 2x, blood sample all visits, questionnaires all visits, GCA assessment all visits.

Follow-Up (2 visits): blood sample 1x

In case of early withdrawal the assessments under 3) will be repeated once.

The most common side effects of TCZ are common colds, sinusitis, and throat infection. Other common side effects are abdominal pain, mouth ulceration, rash, stomach upset, an increase in blood pressure, weight increase, headache, dizziness, cough, shortness of breath, conjunctivitis, and swelling of the legs, ankles and/or feet.
In addition, the following problems may be experienced: diverticulitis, serious infection cancer (There have been very few reports of cancer in patients treated with TCZ. However, a potential risk for development of cancer cannot be excluded), increases in liver enzymes, blood cholesterol increases, decreases in neutrophil/white blood cell counts, decreases in platelet counts, yypersensitivity reactions and anaphylaxis, and demyelinating disorders.

Potential side effects of Prednisone are nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, and acne. The following side effects are less likely to occur: muscle pain/cramps, irregular heartbeat, weakness, swelling of the hands/ankles/feet, unusual weight gain, signs of infection, vision problems (such as blurred vision), vomit that looks like coffee grounds, black bloody stools, severe stomach/abdominal pain, mental/mood changes (such as depression, mood swings, agitation), slow wound healing, thinning skin, bone pain, menstrual period changes, puffy face, seizures, and easy bruising/bleeding. Also the blood sugar level may rise, which can worsen/cause diabetes.

Possible risks of blood drawing and tuberculosis skin test: pain, bruising, infection, dizziness, upset stomach, or fainting.
Possible risks of X-Rays: a slight chance of excessive exposure of radiation with chest x-rays (about the same as the average person receives from background radiation in 10 days).

Possible risks of ECG: cold sticky pads, redness, itching, and potentially irritation from shaving.

The reproductive risk is unknown, so contraception should be used.

Contacts

Public
Hoffmann-La Roche

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Basel 4070
CH
Scientific
Hoffmann-La Roche

Grenzacherstrasse 124
Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Able and willing to provide written informed consent and to comply with the study protocol
- Diagnosis of GCA
- New-onset or refractory active disease

Exclusion criteria

- Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization
- Transplanted organs (except corneal transplant performed more than 3 months prior to screening)
- Major ischemic event, unrelated to GCA, within 12 weeks of screening

- Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to Campath (alemtuzumab), anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
- Treatment with IV gamma globulin or plasmapheresis within 6 months of baseline
- Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
- Previous treatment with TCZ
- Immunization with a live/attenuated vaccine within <= 4 weeks prior to baseline
- Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or MMF within 4 weeks of Baseline
- Treatment with etanercept within 2 weeks; infliximab, certolizumab, golimumab, abatacept, or adalimumab within 8 weeks; or anakinra within 1 week of baseline
- Previous treatment with tofacitinib
- Treatment with cyclophosphamide within 6 months of baseline
- Patients requiring systemic CS for other conditions other than GCA, which, in the opinion of the investigator, would interfere with adherence to the fixed CS taper regimen and/or to assessment of efficacy in response to the test article
- Chronic use of systemic CS for > 4 years or inability, in the opinion of the investigator, to withdraw CS treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency
- Receipt of > 100 mg daily intravenous methylprednisolone within 6 weeks of baseline
- Active TB requiring treatment within the previous 3 years
- Females of childbearing potential and females who are breastfeeding

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:	Recruitment stopped
Start date (anticipated):	09-01-2014

Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Encorton
Generic name:	Prednisone
Product type:	Medicine
Brand name:	Prednisone Tablets USP, 1 mg
Generic name:	Prednisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisone Tablets USP, 2.5 mg
Generic name:	Prenisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisone Tablets USP, 5 mg
Generic name:	Prednisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	tocilizumab SC
Generic name:	tocilizumab SC
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-05-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	12-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	29-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2011-006022-25-NL
ClinicalTrials.gov	NCT01791153
CCMO	NL42377.042.13