A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Patients with Giant Cell Arteritis

Published: 26-08-2015
Last updated: 19-04-2024

Part A: 52-week double-blind treatment phasePrimary* To investigate the efficacy of sirukumab (100 mg q2w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen Secondary* To assess cumulative...

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

Summary

ID

NL-OMON45005

Source
ToetsingOnline

Brief title
GSK RAD 201677

Condition

- Vascular disorders NEC

Synonym
giant cell arteritis, temporal arteritis

Research involving

Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: Industry: GSK

Intervention

Keyword: Giant Cell Arteritis, Sirukumab

Outcome measures

Primary outcome

Part A: 52-week double-blind treatment phase

* Proportion of subjects in sustained remission at Week 52, defined as having

achieved all of the following:

1. Remission* by Week 12 and

2. Absence of disease flare** following remission at Week 12 through Week 52 and

3. Completion of the assigned prednisone taper protocol and

4. No requirement for rescue therapy at any time through Week 52

*Remission is defined as absence of clinical signs and symptoms of GCA and

normalization of ESR [<30mm/hr] and CRP [<1mg/dL])

**Flare is defined as recurrence of symptoms attributable to active GCA, with

or without elevations in ESR and/or CRP

Secondary outcome

Part A: 52-week double-blind treatment phase

* Median and cumulative prednisone dose over time

* Proportion of subjects in sustained remission at Week 52

* Proportion of subjects in remission over time

* Time to first GCA flare after clinical remission

* Number of disease flares per patient over time

* Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare

* Incidence of adverse events and serious adverse events, incidence of corticosteroid-related adverse events, changes in vital signs, hematology and clinical chemistry parameters

* Patient reported outcomes including SF-36v2, EQ-5D (3L), FACIT-Fatigue, Pain VAS, Steroid Impact PRO, HAQ-DI, PGIC

* Change from baseline in ESR over time

* Change from baseline in serum CRP over time

* Serum concentrations of sirukumab

* Serum anti-sirukumab antibodies

* Change from baseline in IFN-* and IL-17A

* Change from baseline in serum markers of bone formation/resorption: CTX1/P1NP

* Correlation of genetic markers with the safety and efficacy response to sirukumab

Part B: 104-week long-term extension phase

* Proportion of subjects who remained in sustained remission 6 months post cessation of 12-month sirukumab treatment

* Proportion of subjects in remission over time

* Time to first GCA flare for subjects in sustained remission at baseline of Part B

* Number of disease flares per patient over time

* Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare

* Patient reported outcomes including SF-36v2, EQ-5D (3L), FACIT-Fatigue, Pain VAS, Steroid Impact PRO, HAQ-DI

* Median and cumulative prednisone dose over time

* Incidence of adverse events and serious adverse events, changes in vital signs, hematology and clinical chemistry parameters

* Incidence of corticosteroid-related adverse events

* Serum anti-sirukumab antibodies

Study description

Background summary

Multiple lines of evidence support a role for interleukin-6 (IL-6) in the pathophysiology of giant cell arteritis (GCA). Sirukumab is a human anti-IL-6 immunoglobulin IgG1kappa monoclonal antibody (mAb) with a high affinity and specificity for binding to the human IL-6 molecule that may have therapeutic benefit in the treatment of GCA by interruption of multiple pathogenic pathways. The purpose of this study is to evaluate the efficacy and safety of sirukumab to characterize the benefit-to-risk profile of sirukumab in the treatment of active GCA.

Study objective

Part A: 52-week double-blind treatment phase

Primary
* To investigate the efficacy of sirukumab (100 mg q2w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen

Secondary
* To assess cumulative prednisone doses in subjects treated with sirukumab plus prednisone as compared to placebo plus prednisone
* To investigate the efficacy of sirukumab (100 mg q2w for 12 months) administered with a 3-month prednisone treatment regimen versus placebo administered with a 6-month prednisone treatment regimen
* To investigate the efficacy of sirukumab (100 mg q2w for 12 months) administered with a 6-month prednisone treatment regimen as compared to placebo administered with a 12-month prednisone treatment regimen (standard of care)
* To investigate the efficacy of sirukumab (100 mg q2w for 12 months) administered with a 3-month prednisone treatment regimen versus placebo administered with a 12-month prednisone treatment regimen
* To investigate the efficacy of sirukumab (50 mg q4w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen
* To investigate the efficacy of sirukumab (50 mg q4w for 12 months) administered with a 6-month prednisone treatment regimen as compared to placebo administered with a 12-month prednisone treatment regimen
* To characterize remission and disease flare over time
* To evaluate the safety of sirukumab plus prednisone treatment compared to placebo plus prednisone treatment
* To investigate corticosteroid-related toxicities
* To assess the effect of sirukumab treatment on health-related quality of life, GCA and/or steroid-related symptoms and disability by patient reported outcomes
* To characterize changes in biomarkers of disease activity

Pharmacokinetic/Immunogenicity
* To investigate the pharmacokinetics of subcutaneously administered sirukumab
* To evaluate immunogenicity of subcutaneously administered sirukumab

Exploratory
* To explore the effect of sirukumab on exploratory biomarkers of Th1 and Th17 cell function
* To evaluate the effect of sirukumab on exploratory biomarkers of bone metabolism

Pharmacogenetic
* To potentially explore relationships between genetic variants and sirukumab efficacy and safety endpoints

Part B: 104-week long-term extension phase

* To evaluate the long-term maintenance of disease remission on cessation of 12 months of sirukumab treatment
* To assess the effect of sirukumab treatment on health-related quality of life, GCA and/or steroid-related symptoms and disability by patient reported outcomes
* To assess long-term cumulative prednisone doses
* To assess the long-term safety of sirukumab
* To investigate long-term corticosteroid-related toxicities
* To evaluate immunogenicity of subcutaneously administered sirukumab in subjects receiving open-label sirukumab

Study design

This is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of sirukumab in the treatment of GCA. The study will be conducted in 2 distinct parts (Part A and Part B) and consists of the following phases:
* A screening phase of up to 6 weeks in duration.
* Part A: a 52-week double-blind treatment phase to establish the efficacy and safety of sirukumab in the treatment of GCA.
* Part B: a 104-week long-term extension phase with the option to receive open-label sirukumab (up to a 52-week duration of open-label treatment) for subjects with active disease at the end of Part A, subjects who have not been able to follow the prednisone taper during Part A, or those who newly flare during the first 52 weeks of Part B.
* An up to 16-week follow-up phase to ensure that all subjects are evaluated for safety at least 16 weeks after receiving the last dose of study drug. This will apply to subjects who are withdrawn prematurely from the study or whose open-label treatment with sirukumab in Part B will complete after Week 88. The duration of the follow-up may vary depending on the time point when the last dose of study drug is taken. Only subjects who complete their sirukumab treatment at Week 104 will require the full 16-week follow-up period.
The maximum duration of subject participation (including screening) is 178 weeks. Completion of Part A is defined as completion of the 52 weeks of double-blind treatment. Completion of Part B is defined as completion of the 104 weeks of the extension phase. Completion of the study is defined as completion of both Parts A and B of the study and/or completion of the 16-week follow-up phase if applicable.
Subjects will be randomized to receive sirukumab (100 mg subcutaneous [SC] every 2 weeks [q2w] or 50 mg SC every 4 weeks [q4w] or matching placebo. All subjects will receive prednisone during the 52-week double-blind treatment period according to a pre-specified taper regimen.
An Independent Data Monitoring Committee (IDMC) and an independent Clinical Events Committee (CEC) will be utilized in this study.

Intervention

In Part A, eligible subjects will be randomized in a ratio of 3:3:2:2:2 to one of the following 5 treatment arms:
1. Treatment Arm A: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen
2. Treatment Arm B: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 3-month prednisone taper regimen
3. Treatment Arm C: Sirukumab 50 mg SC q4w for 52-weeks plus a pre-specified maximum of 6-month prednisone taper regimen
4. Treatment Arm D: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen
5. Treatment Arm E: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 12-month prednisone taper regimen.

The prednisone tapering schedule will be initiated at randomization for all subjects. The pre-specified maximum tapering schedule to be followed will depend on the subject*s treatment group assignment. The prednisone taper will be unblinded (open-label) and will consist of identical weekly decreases in dose for all subjects until a dose of 20 mg/day is reached, at which point the blinded portion of the prednisone tapering regimen will commence.
All subjects who complete Part A of the study will be eligible to enter Part B. The two populations of subjects expected to enter into Part B are:
* Subjects in remission at the primary 52-week endpoint. These subjects will discontinue blinded study drug treatment on entry into Part B and will be followed for maintenance of response. However, they will have the option to receive open-label sirukumab 100 mg SC q2w for a maximum of 52 weeks during the first 52 weeks of Part B in the event of a flare.
* Subjects with disease activity at the primary 52-week endpoint or subjects who have not been able to follow the prednisone taper during Part A. Upon entry into Part B, these subjects will have the option to receive open-label sirukumab 100 mg SC q2w for a maximum of 52 weeks.

For subjects who newly flare at any time during the 1st 52 weeks of Part B and require a treatment change, open-label sirukumab 100 mg SC q2w can be initiated within the first 52 weeks of Part B. The duration of treatment will be at the discretion of the investigator but must not exceed 52 weeks. Treatment with open-label sirukumab 100 mg SC q2w must complete by Week 104 (the end of the extension phase). Corticosteroid use or the initiation of methotrexate therapy alone or in addition to sirukumab treatment during Part B will be at the discretion of the investigator.

Study burden and risks

Burden:
- Questionnaire(s): every visit

- Self administration of study drug: every 2 weeks

See also section '7. STUDY ASSESSMENTS AND PROCEDURES' of protocol dd 11 May 2015.

Risks:

Very common risks of sirukumab: Abnormal liver blood tests

Common risks of sirukumab: Low number of white blood cells, low number of platelets, increase in cholesterol levels, reaction at the site of the injection such as skin redness, itching, swelling or rash

Uncommon risks of sirukumab: Serious infections of the skin, abscess under the skin, infections of the bone, pneumonia, severe infection throughout the body (sepsis), allergic reactions, high blood fat (triglycerides), perforation in stomach or intestines, infections between the disks in the spine.

Contacts

Public
GlaxoSmithKline

Iron Bridge Road 1-3
Stockley Park West, Uxbridge, Middlesex UB11 1BU
GB
Scientific
GlaxoSmithKline

Iron Bridge Road 1-3
Stockley Park West, Uxbridge, Middlesex UB11 1BU
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:
* Age *50 years.
* History of ESR * 50 mm/hour or CRP * 2.45 mg/dL.
* Presence of at least one of the following:
* Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication).
* Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
* Presence of at least one of the following:
* Temporal artery biopsy revealing features of GCA.
* Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), ultrasound (UT) or positron emission tomography-computed tomography (PET-CT)
* Evidence of temporal artery vasculitis on US (for US imaging qualified centers only).;2. Active GCA within 6 weeks of Randomization (Baseline) where active disease is defined by an ESR *30 mm/hr or CRP * 1 mg/dL (*10 mg/L) AND the presence of at least one of the following:
* Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia, or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]).
* Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
* Other features judged by the clinician investigator to be consistent with GCA or PMR flares (i.e., new or worsened extremity claudication, fever of unknown origin).;3. At screening, receiving or able to initiate prednisone treatment with a minimum dose of 20mg/day for the treatment of active GCA. Subjects not currently receiving prednisone treatment must commence dosing (minimum 20 mg/day of prednisone) at the screening visit.;4. Clinically stable GCA disease at baseline such that the subject is able to safely participate in the blinded prednisone taper regimen in the opinion of the investigator.;5. Practicing acceptable methods of birth control as follows:
Males:
Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 months after the last dose of study medication:
a. Vasectomy with documentation of azoospermia.

b. Male condom plus female partner use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of
Childbearing potential.
Male subjects should also not donate sperm from the time of first dose of study medication until 4 months after the last dose of study medication.;Females:
Female subjects of child-bearing potential must use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing potential.;6. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:
a. No history of active or latent TB infection.
b. A negative diagnostic TB test at Screening defined as a negative QuantiFERON Gold test (NB: 2 successive indeterminate QuantiFERON tests
will be considered as a positive result). In cases where an initial indeterminate QuantiFERON test result may be related to sample processing issues, the second QuantiFERON test may be performed at either the local laboratory or the central laboratory at the discretion of the investigator. Re-testing is only permitted for indeterminate results. If the re-test also produces an indeterminate result, further re-testing to determine study eligibility is not permitted either at the local or central laboratory.
c. Chest radiograph (both posterior-anterior and lateral views unless local guidelines recommend only a single view), taken within 12 weeks prior to
baseline or at Screening, and read locally by a qualified radiologist, with no evidence of current active or previous inactive pulmonary tuberculosis.
NB: If there has been recent close contact with persons who have active TB prior to study enrolment the subject will be referred to a TB physician to undergo additional evaluation.

Exclusion criteria

1. Are pregnant or breastfeeding.
2. Recent (within the past 12 weeks) or planned major surgery that would impact on study procedures or assessments.
3. Organ transplantation recipients (except corneas within 3 months prior to baseline visit).
4. Had prior treatment with any of the following:
* Systemic immunosuppressives, including azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, oral or parenteral gold, and IL-1ra (anakinra) within 4 weeks of baseline.
* Biologic agents targeted at reducing TNF (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab) within 2-8 weeks of baseline, depending on the agent *.
* Anti-IL-6 (tocilizumab or any other anti-IL-6 agent) if:
* Used within 8 weeks of randomization
* Associated with a history of intolerance that precluded further treat
* Associated with an inadequate response to 3 months of therapy
* B-cell depleting agents (eg, rituximab) within 12 months prior to baseline or longer if B cell counts have not returned to normal range or baseline levels.
* Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other

alkylating agents within 4 weeks of baseline.
* Abatacept within 8 weeks of baseline.
* Tofacitinib within 4 weeks of baseline.
* Methotrexate use within 2 weeks of baseline.
* Methylprednisolone > 100 mg/day IV (or equivalent) within 8 weeks of baseline.
5. History of severe allergic reactions to monoclonal antibodies, human proteins, or excipients.
6. Evidence of serious concomitant disease, which in the opinion of the investigator makes them unsuitable for participation in the study.
7. Major ischemic event, unrelated to giant cell arteritis, within 12 weeks of screening.
8. Marked baseline prolongation of QTc interval * 480 msec (QTcB or QTcF) or QTc > 500 msec in subjects with Bundle Branch Block **, history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block.
**The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.
9. Current liver disease that could interfere with the trial as determined by the physician investigator.
10. History of or current active diverticulitis, inflammatory bowel disease, or other symptomatic GI tract condition that might predispose to bowel perforation.
11. History of known demyelinating diseases such as multiple sclerosis or optic neuritis.
12. Active infections, or history of recurrent infections or have required management of acute or chronic infections, as follows:
* Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria,
* History or suspicion of chronic infection (e.g joint infection).
OR
* Hospitalization for treatment of infection within 60 days of the baseline visit.
OR
* Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 60 days of baseline or oral antimicrobials within 30 days of baseline.
13. Primary or secondary immunodeficiency.
14. HIV infection (positive serology for HIV antibody), hepatitis C (positive serology for hepatitis C antibody confirmed positive by hepatitis C RNA PCR which is reflexively performed).
15. Hepatitis B infection (positive test results for hepatitis B surface antigen or hepatitis B core antibody).
16. Active malignancy or history of malignancy within previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured).
17. Laboratory abnormalities:
* AST or ALT >2.0 × upper limit of normal (ULN).
* Total bilirubin >ULN with the exception of Gilbert*s disease.
* Platelet count <140 × 109/L.
* Hemoglobin <8.5 g/dL.
* WBC count <3.5 × 109/L.

* ANC <2 × 109/L.
* ALC <0.5 × 109/L.
* Serum creatinine * 2.0 mg/dL (SI: positive * 177 µmol/L).
18. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug, during the study, or within 4 months after the last administration of study drug.
19. Any other autoimmune disease (such as SLE, RA, inflammatory arthritis, other vasculitides, scleroderma, polymyositis, dermatomyositis or other similar systemic connective tissue diseases).
20. Uncontrolled psychiatric or emotional disorder, drug abuse, alcohol abuse within past 3 years.
*Please refer to the Study Procedures Manual (SPM) for guidance.
** If seropositive, consultation with a physician with expertise in the treatment of HIV or hepatitis B or C virus infection is recommended.

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):	16-06-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sirukumab

Generic name:	Sirukumab

Ethics review

Approved WMO Date:	26-08-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-02-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-001758-14-NL

Register	ID
ClinicalTrials.gov	NCT02531633
CCMO	NL53916.091.15