A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Anti-TNF-Alpha Therapy

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

Summary

ID

NL-OMON39738

Source
ToetsingOnline

Brief title
SIRROUND

Condition

- Autoimmune disorders
- Joint disorders

Synonym

rheuma, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilaq

Intervention

Keyword: rheumatoid arthritis, sirukumab, subcutaneously

Outcome measures

Primary outcome

* Proportion of subjects who achieve an ACR 20 response at Week 16.

Secondary outcome

* Change from baseline in HAQ-DI score at Week 24

* Proportion of subjects with an ACR 50 response at Week 24

* Proportion of subjects with DAS28 (CRP) remission at Week 24

Study description

Background summary

The past decade has seen the treatment options for RA multiply. Biologic therapies, beginning with anti-TNF Alpha agents in the late 1990*s, have changed the treatment paradigm and opened the field to higher rates of clinical response in RA, substantial improvements in patients* physical function, and inhibition of radiographic progression. Anti-TNF Alpha agents are well-established as the first biologic agent of choice when a patient has failed MTX. Yet, although biologic therapies are quite efficacious in most patients, there are typically 30 to 40% of patients in clinical studies who do not achieve even a 20% response to the biologic agent. Furthermore, biologic therapies also have a number of safety and tolerability issues such as greater degree of immunosuppression leading to serious infections, greater risk for TB, increased risk of developing demyelinating disease, increased risk for lymphopenia (in the case of rituximab), and/or severe injection or infusion

reactions.
A growing proportion of RA patients have an inadequate response to treatment with an anti-TNF Alpha agent, either because they derive too little benefit and/or because there is intolerance or an adverse reaction to the anti-TNF Alpha agent. In a Swedish rheumatology study, approximately 2 years after initiation of therapy, an estimated 75 to 79% of RA patients on an anti-TNF Alpha agent (etanercept, infliximab) were continuing treatment with the same anti-TNF Alpha agent. A more recent analysis of a Swiss RA registry revealed that 58 to 66% of patients were continuing to receive the anti-TNF Alpha agent after 2 years of treatment. Given that RA is a chronic illness that requires ongoing treatment, there is a large unmet medical need for therapies that act through alternative mechanism of action, to be used after anti-TNF Alpha agent is discontinued. Targeting the IL-6 pathway is one effective approach that has been successfully demonstrated by tocilizumab in the anti-TNF Alpha experienced RA population. Treatment of RA with sirukumab potentially offers a human anti-IL-6 ligand antibody with the advantage of more convenient SC administration compared with tocilizumab IV q4 weeks. There are also potential differences in pharmacology, safety, and efficacy between an agent that binds to the soluble and cell-associated IL 6 receptor (tocilizumab) versus one that binds the IL-6 ligand (sirukumab) in the plasma or interstitial fluid. This study will assess the efficacy and safety of sirukumab for the expanding population of RA patients who are refractory to anti-TNF Alpha treatment and is part of the Phase 3 program to evaluate the potential therapeutic benefit of sirukumab in subjects with moderately to severely active RA.

Study objective

The primary objective is to assess the efficacy of sirukumab as measured by the reduction of the signs and symptoms of RA in subjects with active RA who are refractory to an anti-TNF Alpha agent.

The secondary objectives are to assess the following for sirukumab in subjects with active RA who are refractory to anti-TNF Alpha agents:
* Safety
* Physical function
* Population pharmacokinetics
* Immunogenicity
* Pharmacodynamics

Study design

This is a randomized, double-blind, placebo-controlled parallel-group multicenter study of sirukumab in subjects with moderately to severely active RA who are refractory or intolerant to anti-TNF Alpha therapy. Approximately 990 subjects will be randomly assigned in a 1:1:1 ratio to receive treatment with sirukumab placebo SC q2 weeks, sirukumab SC 100 mg q2 weeks, or 50 mg q4

weeks. Subjects in the placebo group will cross over to receive sirukumab at Week 24. The expected duration of the study is 68 weeks. This includes 52 weeks of treatment with study agent and 16 weeks of safety follow-up after the last study agent administration. Upon completion of participation through Week 52, subjects will be eligible to enroll in a long-term safety and efficacy (LTE) study. If they do not participate in the LTE study they will continue into follow-up of approximately 16 weeks after the last study agent administration.

Database locks (DBL) will occur at Weeks 24, 52, and at the end of study. The study will end when the last subject completes the Week 52 visit and transitions into the LTE study OR completes the safety follow-up, whichever is later. The duration of treatment (interval between the first and last administrations of sirukumab or placebo) will be approximately 1 year.

The placebo-controlled portion of the study is through Week 24, when placebo subjects will cross over to active treatment with sirukumab. Individual subjects and investigators will remain blinded for the duration of the study. Subject safety will be monitored through the end of the study as delineated in the Time and Events Schedules in the protocol.

Intervention

The studymedication (or placebo) is administred once per 2 weeks (1 ml) subcutaneously for a period of 52 weken.

Study burden and risks

The possible discomforts, side effects, and risks related to sirukumab treatment are not all known. Not many people have been treated at this time with sirukumab.

Sirukumab is a drug that may change how the body fights infections. People given sirukumab as well as similar medicines have reported infections. Serious infections that may require hospitalization have been reported.
Sirukumab may keep patient from developing a fever when he/she has an infection and therefore, may hide a sign that a patient has.
Signs of an infection may include:
* fever
* headache
* cough
* congestion
* chills
* change in urine frequency or burning feeling while passing urine
* redness or swelling of the skin or a joint
* night sweats

Sirukumab may lower the number of blood cells that help the body fight infection and stop bleeding. Sirukumab may increase certain types of cholesterol and may affect the liver.

Sirukumab will be given as an injection under the skin. After the injection, temporary and common reactions seen at the injection site could include:
* redness
* pain
* itching
* swelling

Allergic reactions can happen from the study medication. Some may be severe. The following can be signs of an allergic reaction:
* chills
* rash or hives
* nausea
* flushing
* light-headedness
* irregular heartbeats
* chest tightness or wheezing
* difficulty breathing or swallowing
* low blood pressure
* swelling in face, lips, tongue and/or throat

Serious allergic reactions called anaphylaxis have been reported with sirukumab.

It is unknown at this time what effect sirukumab may have on vaccines that patients receives while participating in this study.
A patient cannot receive *live* vaccines such as FluMist®, Varicella, BCG during this study or for 4 months after your last dose of study drug.

Sometimes the body can make special antibodies that may increase the risk of an allergic reaction to either sirukumab or other antibody medicines. If a patient has an allergic reaction, he/she may not be able to have these types of medications in the future.

In people taking a similar drug the following have been reported: gastrointestinal perforations (tears in the stomach or intestines) and a certain type of nervous system disorder which may include symptoms such as changes in vision, weakness, numbness or tingling. Medications like this lower the activity of the immune system, so there may be an increased risk of some types of cancers if the immune system cannot stop them.

Risk of Procedures:
The patient may experience discomfort when a needle is inserted into the vein to collect blood. There may be a

* slight bruise
* discoloration
* swelling
* scarring at the puncture site
* fainting

Over the course of the entire study 371 ml blood (approximately 1.5 cups) will be collected from the patient.

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

1. Be a man or a woman of 18 years of age or older. ;2. Have a diagnosis of rheumatoid arthritis (RA) for at least 3 months before screening;3. Have moderately to severely active RA

with at least 4 of 68 tender joints and 4 of 66 swollen joints, at screening and at baseline;4. Have had anti-tumor necrosis factor (TNF)-alpha therapy and were unresponsive by 1 of the following 2 reasons: Lack of benefit to at least 1 anti-TNF-alpha biologic therapy, as assessed by the treating physician, after at least 12 weeks of etanercept, yisaipu, adalimumab, golimumab, or certolizumab pegol therapy and/or at least a 14-week dosage regimen (ie, at least 4 doses) of infliximab; Intolerance to at least 2 anti-TNF-alpha biologic therapies, as assessed by the treating physician, to etanercept, yisaipu, adalimumab, golimumab, certolizumab pegol, or infliximab or have documented intolerance to an anti-TNF-alpha agent as described above that precludes further administration of anti-TNF-alpha agents;5. If using oral corticosteroids, must be on a stable dose lower than or equal to 10 mg/day of prednisone for at least 2 weeks prior to the first administration of study agent. If currently not using corticosteroids, must not have received oral corticosteroids for at least 2 weeks prior to the first administration of study agent;6. If using non nonsteroidal anti-inflammatory drug (NSAIDs) or other analgesics for RA, must be on a stable dose for at least 2 weeks prior to the first administration of study agent;7. If using non-biologic DMARDs such as methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine, chloroquine, or bucillamine, must be on a stable dose for at least 4 weeks prior to the first administration of study agent and should have no serious toxic side effects attributable to the DMARD;8. Screening C-reactive protein (CRP) levels higher than or equal to 8.00 mg/L or ESR of higher than or equal to 28mm/hr;9. Subjects must meet 1 of the following 3 criteria prior to the first administration of study agent: (a) Anti-CCP antibody-positive at screening, (b) RF positive at screening, or (c) documented history of radiographic evidence of erosive RA in hands or feet prior to the first administration of study agent. ;10. Women, sexually active or otherwise capable of pregnancy, must practice a method of birth control, including abstinence, intrauterine device, double barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel) consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. If using hormonal contraceptives, including oral, injections and patches, a secondary method of contraception must be used. Contraception must be used for the duration of their participation in the study, and for 4 months after the last study agent administration. The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control. ;11. Men, if sexually active with women capable of pregnancy of child bearing potential, are to use an effective method of birth control and to not donate sperm during the study and for 4 months after the last study agent administration. The exception to this restriction is if the subject or his female partner is sterilized; this situation does not require birth control.;12. Be willing and able to adhere to (a) the prohibitions and restrictions specified in this protocol (b) the study visit schedule.;13. Be able to read, understand, and complete study questionnaires.;14. Sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. ;15. Subjects will be included according to the following TB screening criteria:

a. Have no history of latent or active TB prior to screening unless currently receiving treatment for latent TB and there is no evidence of active TB. An exception is made for subjects who have a history of latent TB (defined for the purposes of this study as having had a positive result from either the tuberculin skin test (Appendix B) or the QuantiFERON TB Gold test prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent under this protocol. These subjects do not need to be retested with the QuantiFERON-TB Gold test (or

PPD) during screening. Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local guidelines for immunocompromised patients exist, US guidelines must be followed. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study agent.
d. Within 6 weeks of the first administration of study agent, have a negative QuantiFERON-TB Gold test result or have a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study agent. A negative tuberculin skin test or a newly identified positive tuberculin skin test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study agent is additionally required if the QuantiFERON-TB Gold test is not approved/registered in that country. An exception is made for subjects who have a history of latent TB (a positive result from either the tuberculin skin test or the QuantiFERON TB Gold test prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent. These subjects do not need to be retested with the QuantiFERON-TB Gold test (or PPD) during screening. Subjects with repeatedly indeterminate QuantiFERON-TB Gold test results from 2 samples tested in screening are ineligible.
e. Have a chest radiograph (both posterior-anterior (PA) and lateral view[s] unless local guidelines recommend only a single view), taken within 3 months of the first administration of study agent and read by a qualified pulmonologist or radiologist, with no evidence of current, active TB or old, inactive TB.;16. Sign the informed consent form (ICF) for pharmacogenetics research indicating willingness to participate in the pharmacogenetics component of the study (in order to participate in the optional pharmacogenetics component of this study) where local regulations permit. Refusal to give consent for this component does not exclude a subject from participation in the clinical study.

Exclusion criteria

1.
a. Has received infliximab within 8 weeks of the first study agent administration.
b. Has received golimumab, adalimumab, or certolizumab pegol, within 6 weeks of the first study agent administration.
c. Has received etanercept, or yisaipu within 4 weeks of the first study agent administration;Anti-TNF* therapy : Treatment prior to first study agent administration:
Infliximab, infliximab biosimilar : 8 weeks
Golimumab, adalimumab, certolizumab pegol : 6 weeks
Etanercept, yisaipu : 4 weeks;2.

a. Has a history of intolerance to tocilizumab that precluded further treatment with it, or inadequate response to 3 months of tocilizumab (anti-IL-6 receptor) therapy. Has used tocilizumab within 8 weeks of the first study agent administration.
b. Has used B-cell-depleting therapy (eg, rituximab) within 7 months of first study agent administration or have evidence during screening of abnormally low B-cell level caused by previous B-cell depletion therapy
c. Has used anakinra within 1 week of first study agent administration
d. Has used abacept or any other biologic therapy for the treatment of RA within 8 weeks of the first study agent administration;3. Has received intra-articular (IA), intramuscular (IM), or intravenous (IV) corticosteroids for RA, including adrenocorticotrophic hormone during the 4 weeks prior to first study agent administration;4. Has received leflunomide within 24 months before the first study agent administration and has not undergone a drug elimination procedure, unless the M1 metabolite is measured and is undetectable. If a drug elimination procedure is performed during screening, the M1 metabolite should be measured and found to be undetectable.;5. a. Has a history of cyclophosphamide or cytotoxic agent use
b. Has received cyclosporine A, azathioprine, tacrolimus, mycophenolate mofetil, oral or parenteral gold, or D-penicillamine within 4 weeks of the first study agent administration
c. Has received an investigational drug (including investigational vaccines) or used an investigational medical device within 3 months or 5 half lives, whichever is longer, before the first study agent administration ;6.Has screening laboratory test result as follows:
a. Hemoglobin < 8.5 g/dL (International System of Units [SI]: < 85 g/L) or < 5.3 mmol/L.
b. WBCs < 3.5 × 103 cells/*L (SI: < 3.5 × 109 cells/L).
c. Neutrophils < 1.95 × 103 cells/*L (SI: < 1.95 × 109 cells/L).
d. Platelets < 140 × 103 cells/*L (SI: < 140 × 109 cells/L).
e. Serum ALT or AST > 1.5 times the ULN for the central laboratory conducting the test.
f. Total bilirubin > ULN
g. Serum creatinine higher than or equal to 2.0 mg/dL (SI: higher than or equal to 177 *mol/L).;7. Has current signs or symptoms of severe, progressive, or uncontrolled active inflammatory arthritis other than RA, renal, hepatic, dermatologic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, or neurologic disease. Hospitalization for a cardiovascular event (myocardial infarction, unstable angina, stroke, TIA within 3 months prior to the first administration of study agent is exclusionary.;8. Has known allergies, hypersensitivity, or intolerance to sirukumab or its excipients (refer to Investigator's Brochure).;9. Has a history of severe allergic reaction to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients.;10. Has a marked baseline prolongation of the QTc interval * 450 msec (either QTcB or QTcF, machine or manual overread, males or females), a history of risk factors for Torsade de Pointes such as persistent hypokalemia or family history of long QT syndrome; or a history of second- or third-degree heart block.;11. Has had a severe infection (including, but not limited to hepatitis, pneumonia, sepsis, or pyelonephritis); or has been hospitalized for an infection; or has been treated with IV antibiotics for an infection, within 2 months prior to the first administration of study agent. ;12. Has a history of chronic or recurrent infectious disease or ongoing infection including, but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic non-remitting cystitis), or open, draining skin wound or an ulcer.;13. Has a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.;14. Has a history of known demyelinating diseases such as multiple sclerosis or

optic neuritis.;15. Has a history of gastrointestinal perforation or currently has active diverticulitis.;16 Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening. Is infected with HIV (positive serology for HIV antibody) or hepatitis C (positive serology for Hep C antibody). If seropositive, consultation with a physician with expertise in the treatment of HIV or hepatitis C virus infection is recommended. ;18. Is infected with hepatitis B virus. For subjects who are not eligible for this study due to HBV test results, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended. ;19. Have any known malignancy or has a history of malignancy within the previous 5 years (with the exception of a nonmelanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months before the first study agent administration or cervical neoplasia with surgical cure).;20. Has uncontrolled psychiatric or emotional disorder, including a history of drug and alcohol abuse within the past 3 years that might prevent the successful completion of the study.;21. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 4 months after the last administration of study agent. Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.;22. Is pregnant or breast-feeding.;23. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.;24. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-07-2013

Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CNTO 136
Generic name:	sirukumab (50 and 100 mg)

Ethics review

Approved WMO Date:	13-12-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-04-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-08-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	08-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
Other	NCT01606761
EudraCT	EUCTR2010-022243-38-NL
CCMO	NL42625.098.12