A Phase 2b, Dose-ranging Study to Evaluate the Efficacy and Safety of Sifalimumab in Adults with Systemic Lupus Erythematosus

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

Summary

ID

NL-OMON35833

Source
ToetsingOnline

Brief title
Dose repsonse study with sifalimumab in SLE

Condition

- Autoimmune disorders

Synonym
lupus, SLE

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca

Source(s) of monetary or material Support: Bedrijven

Intervention

Keyword: autoimmune disease, interferon alpha, lupus, SLE

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the efficacy of sifalimumab compared to placebo in subjects with chronic, moderately-to-severely active SLE with an inadequate response to SOC SLE at Day 365 (Week 52).

Secondary outcome

The secondary objectives of this study are:

1) To evaluate the effect of sifalimumab compared to placebo in reducing background oral corticosteroids dosage

2) To evaluate the effect of sifalimumab compared to placebo in improving inflammatory cutaneous lupus lesions

3) To evaluate the effect of sifalimumab compared to placebo in improving fatigue

4) To evaluate the safety profile of sifalimumab

Study description

Background summary

There is substantial unmet medical need in the treatment of SLE, particularly in patients with moderate to severe disease. Many agents currently used to treat SLE such as azathioprine, cyclophosphamide, and mycophenolate mofetil/mycophenolic acid have not been approved for the disease. Other available treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics for fever, arthralgia, and

arthritis; and topical sunscreens to minimize photosensitivity. Antimalarial agents (eg, hydroxychloroquine) and corticosteroids may be added to control arthralgia, arthritis, and rashes. It is often difficult to taper patients with moderate or severe disease completely off corticosteroids, which cause long-term morbidity and may contribute to early cardiovascular mortality (Petri, 2001; Urowitz et al, 1976). Even low-dose prednisone, if used as a long-term treatment, carries increased risk for side effects (Petri, 2001).

There is an increasing body of data from multiple investigators indicating a pivotal role for type I IFN, especially IFN-α, in the genesis and maintenance of active SLE (Baechler et al, 2003; Baechler et al, 2004; Crow, 2003; Dall'era et al, 2005; Kirou et al, 2005). Sifalimumab (also known as MEDI-545) is a human immunoglobulin G1 kappa (IgG1*) monoclonal antibody (MAb) that binds to and neutralizes a majority of the subtypes of human IFN-α.

Clinical studies with sifalimumab in subjects with SLE have yielded promising results thusfar. To date, sifalimumab has been found to have an acceptable safety profile in adult subjects with mildly-to-moderately active SLE following single-dose IV administration (Study MI-CP126) as well as in adult subjects with moderate to severe disease (SLEDAI-2K >= 6 points at screening) following multiple-dose IV administration (Study MI-CP152). Results from Study MI-CP152, a multicenter randomized, double-blind, placebo-controlled dose escalation study, has provided additional safety, PK, PD and clinical activity data that supports further clinical development of sifalimumab in subjects with moderately-to-severely active SLE.

Study objective

The aim of the study is to evaluate the efficacy and safety of three IV treatment regimens of sifalimumab in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to SOC SLE (Standard Of Care treatment for SLE). Efficacy will be compared to placebo, with all treatment groups receiving SOC SLE. This study is also intended to assess the safety, including immunogenicity (IM), of sifalimumab in this subject population.

Study design

The design of this study is:
• multinational
• multicenter
• randomized
• double-blind
• placebo-controlled
• parallel group

Intervention

Subjects will be randomized in a 1:1:1:1 ratio to receive a fixed IV dose of sifalimumab (200, 600, or 1200 mg) or placebo as follows:
• Treatment Arm 1 (n = 136): IV Sifalimumab (200 mg) for 48 weeks
• Treatment Arm 2 (n = 136): IV Sifalimumab (600 mg) for 48 weeks
• Treatment Arm 3 (n = 136): IV Sifalimumab (1200 mg) for 48 weeks
• Treatment Arm 4 (n = 136): IV Placebo for 48 weeks

Investigational product (sifalimumab or placebo) will be administered as a fixed dose every 2 weeks (14 days) for the first 3 doses (Days 1, 15, and 29) and then every 4 weeks (28 days) thereafter for 11 doses (Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337) for a total of 14 doses. Investigational product will be administered as an IV infusion, via an infusion pump, over 60-90 minutes, depending on the subject*s weight on the day of dosing.

Study burden and risks

In this study subjects will receive an infusion with the study drug sifalimumab (200, 600 or 1200 milligram) or placebo. The infusion will take between 60 and 90 minutes to administer. Subjects need to attend for visits more frequently (during 18 months once every 4 weeks with an additional visit 2 weeks after the first infusion - only the last visit occurs 3 months after the previous visit - 19 visits in total). The visits take 2 to 4 hours because various tests and assessments need to be done. Subjects will be asked to fast for a couple of visits (without having breakfast). This is needed to measure properly for example cholesterol in blood.

Risks and discomforts:
• Restriction to become pregnant/ make your partner pregnant during the study till 180 days after the last infusion with study treatment.
• Infusion reaction (anaphylaxis)
• Infections
• Completion of questionnaires during visits.
• Cervical smear: At the start and end of the study a smear test of the cervix will be performed. A smear test may be unpleasant.
• Blood sampling: May cause pain, bleeding, and/or bruising when blood is taken, occasional light-headedness and rarely, development of infection. In total approximately 625 ml blood will be taken.
• X-ray: An X-ray exposes the subject to a small amount of radiation.
• Skin photography: Photographs of active skin lesions will be taken. These photographs will be taken in a way that will not identify the subject.

Side Effects:
• Systemic Lupus Erythematosus (worsening)

• Urinary Tract Infection
• Nausea
• Nasopharyngitis
• Lymphocyte Count Decreased
• Headache
• Diarrhea
• Arthralgia
• Upper Respiratory Tract Infection

Additional events:
• Back pain
• Arm or leg pain
• Pneumonia
• Bronchitis
• Peripheral edema
• Infusion reactions
• Increase in white blood cells
• Increase in blood sugar
• Insomnia
• Pruritis
• Blood count changes

Contacts

Public
Astra Zeneca

Postbus 599
2700 AN Zoetermeer
NL
Scientific
Astra Zeneca

Postbus 599
2700 AN Zoetermeer
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet all of the following criteria:
1. In the opinion of the investigator, must have adequate reading and writing abilities such that the subject can comprehend and complete the informed consent, and all protocol-related subject assessments.
2. Age 18-75 years at the time of screening.
3. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
4. Fulfils at least 4 of the 11 American College of Rheumatology classification criteria for SLE, one of which must be:
a) Significantly positive antinuclear antibody test at screening; OR
b) Elevated anti-dsDNA or Sm antibody at screening.
5. Weight >= 40.0 kg at screening.
6. Diagnosis of pediatric or adult SLE with chronic disease activity requiring ongoing treatment or observation for >= 24 weeks (>= 168 days) prior to screening.
7. Currently receiving at least one of the following:
a) A stable dose of oral prednisone (or equivalent) <= 20 mg/day from at least 2 weeks (14 days) prior to signing of the informed consent through Day 1.
b) Any of the following medications administered at a stable dose for a minimum of 8 weeks (56 days) prior to signing of the informed consent through Day 1: azathioprine, antimalarial (eg. chloroquine, hydroxychloroquine, quinacrine), mycophenolate mofetil/ mycophenolic acid, weekly administrations of oral or sc methotrexate.
8. Prior to Day 1, External Adjudication Group confirmation of both:
(a) At screening, SLEDAI-2K score >= 6 points or *Clinical* SLEDAI-2K score >= 6 points.
(b) At least one of the following: BILAG-2004 Index level A disease in >= 1 body/organ system or BILAG-2004 Index level B disease in >= 2 body/organ systems.
9. Day 1 *Clinical* SLEDAI-2K score >= screening *Clinical* SLEDAI-2K score.
10. Physicians Global assessment >= 1.0 on a 0-3 scale at screening.
11. Females of childbearing potential must use 2 effective methods of avoiding pregnancy, have a sterile male partner, are 1 year postmenopausal, or practicing abstinence.
12. Non-sterilized males must practice two effective contraceptive measures with a female of childbearing potential from Day 1 through at least 180 days after the last dose of investigational product has been administered.
13. Females with an intact cervix must have documentation of a Pap smear with no documented malignancy (eg. CIN III and AIS) within 24 weeks (168 days) prior to Day 1.
14. Willing to abstain from other forms of experimental treatment for SLE during the study.
15. Meets all of the following tuberculosis (TB) criteria:
a) No history of latent or active TB prior to screening with the exception of latent TB within 3

years prior to screening with documented completion of appropriate treatment.
b) No signs or symptoms suggestive of active TB upon medical history or physical examination.
c) No recent contact with a person with active TB OR if there has been such contact, referral to a physician specializing in TB to undergo additional evaluation prior to randomization and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of investigational product.
d) Negative diagnostic TB test within 28 days prior to randomization (defined as a negative QuantiFERON-TB Gold for TB at screening) OR a positive diagnostic TB result (defined as a positive QuantiFERON-TB Gold blood assay for TB obtained during the screening period) for which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either at or before the first administration of investigational product OR a confirmed indeterminate QuantiFERON-TB Gold blood assay for TB obtained during the screening period with ongoing TB QuantiFERON-TB Gold testing at Day 57, Day 169, and Day 253.
e) A chest radiograph with no evidence of current active infection (eg. TB) or old active TB, malignancy, or clinically significant abnormalities (unless due to SLE) obtained during the screening period or anytime within 90 days prior to signing of the informed consent.
16. Adequate peripheral venous access.
17. Ability to complete and meet all requirements for randomization within 28 days after signing the informed consent form.

Exclusion criteria

1. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or confound interpretation of subject safety or study results.
2. Concurrent enrollment in any other clinical study with an investigational product within 4 weeks (28 days) prior to Day 1 or within 5 half-lives of the investigational product used in that clinical study, whichever is longer.
3. Employees of the clinical study site or any other individuals involved with the conduct of the study or immediate family members of such individuals.
4. Receipt of any of the following:
a) Any new oral prednisone therapy (or equivalent) or any change in current oral prednisone dose (or equivalent) anytime from 2 weeks (14 days) prior to signing of the informed consent through Day 1.
b) Any new dose or change in current dose of any of the following anytime in the 8 weeks (56 days) prior to signing of the informed consent through Day 1: azathioprine; any antimalarial (eg. chloroquine, hydroxychloroquine, quinacrine); mycophenolate mofetil/mycophenolic acid; oral methotrexate; or SC methotrexate.
5. Receipt of any of the following:
a) Azathioprine > 150 mg/day.
b) Mycophenolate mofetil/mycophenolic acid > 3.0 grams/day.
c) Oral or SC methotrexate > 20 mg/week.
d) Any change in route of administration of oral or SC methotrexate anytime within the 8 weeks (56 days) prior to signing of the informed consent.

6. Receipt of more than one dose of sifalimumab prior to screening.
7. Receipt of a biologic agent within 5 half-lives or prior to loss of PD and/or clinical effect, whichever is longer, prior to signing of the informed consent form.
8. A known history of allergy or reaction to any component of the investigational product formulation or history of anaphylaxis to any human gamma globulin therapy.
9. Receipt of more than one prescribed NSAID at an anti-inflammatory dose within 2 weeks (14 days) prior to Day 1; OR receipt of fluctuating doses of a prescribed NSAID within 2 weeks (14 days) prior to Day 1.
10. Receipt of any of the following:
a) Intra-articular, intramuscular or intravenous glucocorticoids within 6 weeks (42 days) prior to Day 1.
b) Any live or attenuated vaccine within 4 weeks (28 days) prior to signing the informed consent form (administration of killed vaccines is acceptable).
c) Oral anti-infectives (including antivirals) for active infection within 2 weeks (14 days) prior to Day 1.
d) Bacillus of Calmette and Guérin Vaccine (BCG) within 1 year of signing the informed consent form.
e) Any restricted medication listed in Appendix 3of the protocol.
11. Receipt of any of the following slow-acting immunosuppressants:
a) Etanercept <= 4 weeks (<=28 days) prior to signing the informed consent form.
b) Adalimumab, infliximab, or golimumab <= 12 weeks (<=84 days) prior to signing the informed consent form.
c) Rituximab or belimumab < 24 weeks (<=168 days) prior to signing the informed consent form.
12. Any fluctuation in hormone replacement therapy dose within 8 weeks (56 days) of signing the informed consent form.
13. Active severe or unstable neuropsychiatric SLE that would make the subject unsuitable for the study or unable to fully understand the informed consent, including but not limited to: aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes; acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex.
14. Within 8 weeks (56 days) prior to screening, active severe SLE-driven renal disease or unstable renal disease (eg. clinically significant increase in creatinine or active urinary sediment) that in the opinion of the investigator would make the subject unsuitable for this study.
15. A diagnosis (within 1 year of signing the informed consent form) of mixed connective tissue disease or any history of overlap syndromes of SLE with rheumatoid arthritis, erosive arthritis, or scleroderma.
16. History of, or current, inflammatory joint or skin disease other than SLE that in the opinion of the investigator could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments.
17. History of asthma that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks (14 days) within the last 24 weeks (168 days) prior to randomization.
18. Known history of a primary immunodeficiency or an underlying condition such as human immunodeficiency virus (HIV) infection or splenectomy that predisposes the subject to

infection.
19. Confirmed positive test for hepatitis B surface antigen (HBsAg) serology for:
a) Hepatitis B surface antigen (HBsAg).
b) Isolated Hepatitis B core (HBc) with HBV DNA detected by reflex testing by the central lab at screening or at any time for the duration of the study.
20. Confirmed positive test for hepatitis C serology by central laboratory.
21. Any serious herpes infection at any time prior to randomization, including but not limited to disseminated herpes, herpes encephalitis, or ophthalmic herpes.
22. Any herpes zoster infection that has not completely resolved within 12 weeks (84 days) prior to signing of the informed consent form.
23. Any of the following within 4 weeks (28 days) prior to signing the informed consent form.
a) Clinically significant active infection, including ongoing, and chronic infection (i.e. osteomyelitis, bronchiectasis, etc) but allowing chronic nail infections.
b) Any infection requiring hospitalization or treatment with IV anti-infectives.
24. Lactating or pregnant females or females who intend to become pregnant anytime from initiation of screening through the 180-day safety follow-up period following last dose of investigational product.
25. Current evidence of alcohol, drug or chemical abuse, or a recent history of such abuse < 1 year before randomization into the study.
26. History of cancer, apart from basal cell carcinoma or cervical cancer treated with apparent success with curative therapy >= 1 year before randomization into the study.
27. Major surgery (See Appendix 4) within 8 weeks (56 days) before signing the informed consent form or elective major surgery planned during the study period.
28. Spontaneous or induced abortion, still or live birth, or pregnancy <= 4 weeks (<= 28 days) prior to signing the informed consent form.
29. At screening (within 4 weeks [28 days] before Day 1), any of the following:
a) AST > 2.0 × upper limit of the normal range (ULN) unless, in the opinion of the investigator, it is caused by myositis (with an elevated CPK) associated with SLE.
b) ALT > 2.0 × ULN unless, in the opinion of the investigator, it is caused by myositis (with an elevated CPK) associated with SLE.
c) Total bilirubin > ULN (unless due to Gilbert*s syndrome).
d) Serum creatinine > 2.0 mg/dL.
e) Urine protein/creatinine ratio > 2.0.
f) Neutrophil count < 1,000/µL (or < 1.0 × 109/L).
g) Platelet count < 25,000/µL (or < 25 × 109/L).
h) Hemoglobin (Hgb) < 8 g/dL (or < 80 g/L).
i) Hemoglobin A1c (HbA1c) > 8% (or > 0.08) at screening (diabetic subjects only).

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):	25-01-2012
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not known yet
Generic name:	sifalimumab

Ethics review

Approved WMO Date:	03-05-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-08-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-11-2011

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-06-2012
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	EUCTR2010-024069-30-NL
ClinicalTrials.gov	NCT01283139
CCMO	NL36038.042.11