# A randomised, double-blind, placebo-controlled, multicentre prospective dose-finding Phase II/III study with atacicept given subcutaneously to subjects having recently experienced a flare of systemic lupus erythematosus (SLE)

Published: 16-08-2011
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PRIMAIRYThe primary objective of this trial is to evaluate the efficacy of atacicept compared to placeboin preventing new flares in subjects with SLE.SECONDARYSecondary objectives of the trial are:• To evaluate the safety and tolerability profile of...

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

## Summary

### ID

NL-OMON39295

**Source**
ToetsingOnline

**Brief title**
Atacicept in generalised SLE, Phase II/III (APRIL SLE)

## Condition

- Autoimmune disorders
- Connective tissue disorders (excl congenital)

**Synonym**
SLE, systemic lupus

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Merck BV - An affiliate of Merck Serono S.A.
**Source(s) of monetary or material Support:** MerckSerono International S.A. - an affiliate of Merck KGaA;Darmstadt;Germany

## Intervention

**Keyword:** Atacicept, SLE

## Outcome measures

### Primary outcome

Primary:

The primary efficacy endpoint will be the proportion of subjects experiencing a

new flare (as

defined by a British Isles Lupus Assessment Group [BILAG] score of A or B)

during the 52-

week treatment period following randomisation.

### Secondary outcome

SECONDARY

Secondary efficacy endpoints will include:

• Time to first new flare from randomisation (main secondary endpoint).

• Proportions of subjects within each of the following ordinal response

categories at

Week 52: No flare, first new flare scored as BILAG B and first new flare scored

as

BILAG A.

• Proportion of subjects with a new flare (BILAG A or B) within the initial 24

weeks after

randomisation.

• Corticosteroid exposure post-randomisation.

TERTIAIRY

• Number of flares per subject over 52 weeks.

• Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic

Lupus

Erythematosus Disease Activity Index (SELENA SLEDAI) score over time.

Quality of Life (QOL), as measured by the Krupp Fatigue Severity Scale (KFSS)

and the

Medical Outcomes Study Short Form General Health Survey (SF-36) over time.

• Change from baseline in Systemic Lupus International Collaborating Clinics

(SLICC)

damage score at Week 52.

• Numerical BILAG score over time.

• Proportion of subjects for whom immunosuppressive treatment or high-dose

corticosteroids are initiated during the trial. High-dose corticosteroids are

defined as 20

mg or more of prednisone or equivalent doses of other corticosteroids.

The following tertiary endpoints will be assessed at Week 24 and at Week 52, respectively:

• Changes from baseline in anti-nuclear antibodies (ANA), anti-double-stranded (ds)DNA antibodies and complement levels.

• Proportion of subjects who maintain a BILAG C or BILAG D from randomisation.

• Proportion of subjects with baseline C3 below normal limits who have normal C3 values.

• Proportion of subjects with baseline C4 below normal limits who have normal C4 values.

• Proportion of subjects with positive anti-dsDNA antibody levels at baseline who have negative results.

Safety Endpoints:

• Nature, severity and incidence of adverse events.

• Incidence and severity of laboratory abnormalities.

• Proportion of subjects who develop binding and/or neutralising antibodies to atacicept.

• Electrocardiogram (ECG) monitoring.

• Total immunoglobulin (Ig), Ig subclasses (IgG, IgA and IgM) and lymphocyte subpopulations.

• Changes from baseline in antibody titres for pneumococcus, tetanus and

diphtheria.

Other Endpoints:

Pharmacokinetic Endpoints:

• Free atacicept

• Composite atacicept (defined as free atacicept + atacicept·BLyS complex)

• Total atacicept (defined as free atacicept + atacicept·BLyS complex +

atacicept·APRIL

complex; on treatment evaluation, contingent on availability of appropriate

assays)

• Atacicept·BLyS complex

Pharmacodynamic Endpoints:

• Free APRIL and free BLyS (on treatment evaluation, contingent on availability

of

appropriate assays)

• ESR (performed locally), CRP

• C3, C4

• Anti-dsDNA antibodies, antinuclear antibodies (ANA)

• Total immunoglobulin and immunoglobulin subclasses (IgG, IgA and IgM)

• Lymphocyte subpopulations

Pharmacogenomics Endpoints:

• Distribution of genetic and genomic variations between different

clinically-defined

groups of subjects based on PK profiles, safety and efficacy variables.

# Study description

**Background summary**

SLE is a chronic, usually life-long, potentially fatal autoimmune disease characterised by unpredictable exacerbations and remissions with protean clinical manifestations. In SLE there is a predilection for clinical involvement of the joints, skin, kidney, brain, serosa, lung, heart and gastrointestinal tract. The presence of anti-double stranded DNA antibodies is a hallmark of this disease. Roles for BLyS and APRIL in SLE have been suggested by both animal and human studies.
The aetiology of SLE remains unknown. A genetic predisposition, sex hormones, and environmental factors likely contribute to the disordered immune response that typifies the disease.
The origin of autoantibody production in SLE is unclear, but a role has been suggested for an antigen-driven process, which is characterised by a disturbance of immune regulation that results in B cell hyper-responsiveness and production of autoantibodies and immune complexes that cause chronic inflammation and multiple organ damage.
Subjects with SLE present specific signs and symptoms such as fatigue, arthralgia, skin rashes and headache as well as symptoms that reflect multiple organ involvement. Most subjects with SLE will present involvement of the skin or joints. A common presenting complaint is a photosensitive rash, often associated with alopecia. Arthralgia or frank arthritis is also very common. Subjects may present with fever accompanied by single-organ involvement, such as inflammatory serositis, glomerulonephritis, neuropsychiatric disturbance or haematological disorder (i.e. autoimmune haemolytic anaemia or thrombocytopenia).
There is a very high unmet medical need for novel therapies with improved

risk/benefit ratios that would specifically affect manifestations of SLE and increase subjects*
overall quality of life. New therapeutic agents for SLE
therefore need to reduce the need for corticosteroids and immunosuppressive agents, control
end organ damage, reduce mortality and improve quality of life while having limited side
effects.
Treatment of SLE subjects with atacicept is expected to reduce B cell numbers and by
consequence the level of anti-dsDNA antibodies, thereby ameliorating progression of disease
and survival as seen in murine models.

**Study objective**

PRIMAIRY
The primary objective of this trial is to evaluate the efficacy of atacicept compared to placebo
in preventing new flares in subjects with SLE.

SECONDARY
Secondary objectives of the trial are:
• To evaluate the safety and tolerability profile of atacicept in treated subjects with SLE,
• To confirm the optimal dose of atacicept for treatment of subjects with SLE,
• To gain further information on the effect of atacicept on relevant markers specific to its
mechanism of action (MoA) and their correlation to disease activity/progression,
• To further characterise the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of
atacicept, and
• To identify genetic and genomic variations associated with drug response and disease
activity/progression.

**Study design**

This Phase II/III trial will enrol subjects with SLE who satisfy at least 4 of the 11 ACR
(American College of Rheumatology) criteria and have a disease history of at least six
months. Eligible subjects must have active SLE with at least one BILAG A or B score
(excluding a single B due to haematological values) at screening that requires a change in the

dose of corticosteroids, and must have positive anti-nuclear antibodies at screening.
The subject will enter the initial flare treatment period and will be treated with
corticosteroids according to regimens defined in the protocol (prednisone doses as presented
in the table in Section 6.2.1or equivalent doses of other corticosteroids as per Appendix J).
BILAG will be assessed 10 weeks after the start of corticosteroid treatment. If the subject
improves from BILAG A or B to BILAG C or D within a maximum period of 10 weeks and
if his/her steroid dose remains stable at a level of 7.5 mg prednisone or equivalent for the
2 weeks following observation of BILAG improvement, a further BILAG assessment will be
performed. If this assessment shows no BILAG A or B scores, the subject will be considered
eligible for randomisation. Subjects who do not satisfy all of these criteria will be withdrawn
from the trial; those who experience new BILAG A or B flares during the initial flare
treatment period will also be withdrawn.
At the end of this approximately 13-week period, following confirmation of continued
eligibility for the trial, subjects will be randomised in a 1:1:1 ratio to receive one of two dose
levels of atacicept or placebo, given by subcutaneous (SC) injection.
The treatment period will consist of an initial loading period of 4 weeks, during which the
assigned dose of atacicept or placebo will be administered twice weekly (BIW), followed by
a maintenance period of 48 weeks, during which the assigned dose (75 mg, 150 mg or
placebo) will be administered once weekly (QW). Due to the recent safety issue and protocol amendment 6 resulted in the termination of the 150 mg arm. The patients that received 150 mg were unblinded and stopped the study treatment. The remaining patients are receiving 75 mg or placebo.
Subjects will be assessed before dosing on Study Day 1 (SD 1, defined as the day of first
Investigational Medicinal Product administration), and then at the beginning of Weeks 2, 4,
8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52. Three Follow-up visits will take place at
Weeks 56, 64, and 76 (4, 12 and 24 weeks after the last dose).
In a subset of subjects in selected centres, flow cytometric analyses of B cell subsets, T cells

and NK cells in peripheral blood will be performed to characterise atacicept*s effects on
these cell populations. Pharmacokinetic sampling will also be performed at additional time
points for this subset, which will consist of 50 subjects from each treatment group, including
placebo. All subjects in the participating centres will provide consent for these procedures;
the subjects who will be part of the subset will be registered by the trial*s central
randomisation service.
A BILAG assessment should be performed in case of any suspected flare. If a BILAG A or
B flare is confirmed after a BILAG assessment, the assessments planned for Week 24 will be
performed. Subjects who experience post-randomisation flares can be treated with additional
corticosteroids (at a maximum to dose levels described in Section 6.2.1), NSAIDs and
topical treatment and remain in the trial, provided that post-randomisation flare treatment is
completed within 12 weeks of its initiation. If after this post-randomisation flare treatment
the patient cannot be brought back on the treatment regimens he/she was receiving at
randomisation, the patient must discontinue trial medication and will undergo the 3 followup
visits as described in Section 6.2.5.

**Intervention**

Hiervoor verwijzen wij graag naar de study flowchart in het protocol, pagina 114/115 en pagina 58 van het protocol (dosage and administration).

**Study burden and risks**

In a clinical trial like this one, every risk or side effect cannot be predicted. Each person*s reaction to an experimental drug may be different. You may have a side effect or be at risk for symptoms, illnesses or complications that could not be predicted by your trial doctor or the Sponsor of this trial.
If any side effects occur, you must inform your trial doctor immediately.
Atacicept produced few side effects when tested in small studies in healthy male volunteers and in people with cancer, rheumatoid arthritis (RA) and SLE. The maximum single dose tested by subcutaneous injection was 630 mg and by intravenous injection 1260 mg.
Overall, approximately 800 subjects have received at least one dose of

atacicept with a maximum of 8.5 months in treatment duration in completed clinical research trials (including subjects with systemic lupus erythematosus, lupus nephritis, multiple sclerosis, rheumatoid arthritis, optic neuritis, multiple myeloma, non-Hodgkin*s lymphoma and B cell chronic lymphocytic leukemia).
Some patients treated with atacicept for systemic lupus erythemathous have experienced redness and pain at the site of injection. These reactions were mild or moderate.
Treatment with atacicept also leads to a decrease in the number of cells in the immune system called B-cells and in the levels of antibodies (also called immunoglobulins) in blood. Both of these effects are thought to be important in contributing towards the way that atacicept may help treat certain diseases. Because antibodies and B-cells are also important in helping your body to fight infection, there is an increased risk of mild or moderate upper respiratory tract infections with the treatment with atacicept.
Some side effects of atacicept were observed in atacicept-treated patients with other disease and have, to date, not been observed to be related to atacicept in patients with systemic lupus erythemathous. These are the following:
In patients with multiple sclerosis, atacicept treatment was shown to cause an increase in multiple sclerosis disease activity. Multiple sclerosis is a disease affecting the central nervous system, leading to damage of the outer layer (called myelin) that surrounds nerve cells. This process is called demyelination. Therefore you cannot participate in this trial if you have or have had any demyelinating disease such as multiple sclerosis or optic neuritis. Your study doctor will provide you with more information if needed

Data from previous trials also suggested that exposure to atacicept may increase the risk of allergic angioedema (swelling of the lips, face, mouth or throat, which occurs within minutes or hours, and may be associated with other allergic reactions like urticaria). If you experience such a reaction or other allergic reaction, you should stop injecting atacicept and seek medical attention as soon as possible.

Potential risks
A potential risk is a side effect that has not been confirmed to be related to Atacicept. If any of the side effects mentioned below occur, you must inform your trial doctor immediately.
Two subjects included in this trial who were receiving the high dose of atacicept (i.e 150 mg) have died of a serious infection of the lungs called pneumonia. This high dose has been now discontinued (this means that no patient will receive atacicept 150mg at this time anymore) However, it can not be excluded that exposure to any dose of atacicept may increase your risk of having a similar serious infection.
Because of the effect of atacicept on antibodies and B-cells, treatment with atacicept may increase your risk of infection including vaccine preventable infections.

If you experience any, even mild, symptoms of an infection such as fever, cough, shortness of breath, nasal congestion, headache, muscle and joint aches, diarrhoea, flu-like symptoms, vomiting or any other symptoms of an infection, it is important that you contact your study doctor immediately and are treated swiftly and appropriately. You should stop taking study medication until a proper evaluation by your doctor is completed. Please see the section *Study procedures and requirements* for advice on avoiding infections and for guidance in case you are hospitalised during the study participation.

In a previous study of subjects with severe active lupus nephritis, which is an inflammation of the kidneys leading to loss of protein in the urine, three of the four patients that received atacicept in combination with another recently started treatment consisting of MMF (also called Cellcept or mycophenolate mofetil) and corticosteroids were found to have low levels of immunoglobulins. Two of these patients developed a serious infection of the lungs called pneumonia. If you participate in this study, your antibody levels will be tested every two weeks for the first month and then every month. If your levels of antibodies fall too low, your study doctor will be informed and you will be withdrawn from the study. If you develop fever, cough, shortness of breath, flu-symptoms or chest pain, you should call your study doctor as these can be symptoms of pneumonia.
In addition, if you are currently taking a drug called Cellcept, MMF or mycophenolate mofetil, please tell your study doctor. This drug is not permitted during this trial.

Some serious allergic reactions may be related to atacicept. These may involve dizziness, low blood pressure (loss of consciousness is possible in the case of very low blood pressure), difficulty in breathing and swallowing, heart palpitations, abdominal pain, and vomiting. Prompt medical care is needed since serious allergic reactions may be potentially life-threatening. If you think you are having an allergic reaction, you should get immediate medical attention.

Treatment with atacicept could increase the risk of vertigo, balance problems or other ear disorders. This could make you feel dizzy and lose your balance. If you develop such disorders, you should not drive or operate machinery.

Results of previous trials suggest that atacicept could increase the risk of developing new disturbances to the rhythm of the heart. If you develop such events, you should contact your study doctor or study centre staff as soon as possible.

Because atacicept modifies the immune system, there is a possible risk of inducing new autoimmune diseases or making existing disease worse. However, this has not been observed in previous SLE trials to date.

In other previous trials, very rare adverse events of cancer were observed in subjects treated with atacicept for rheumatoid arthritis, systemic lupus

erythematosus and multiple sclerosis. The possible immunosuppressive effect of atacicept could increase the risk of tumors. However, to date, such a link between atacicept and tumors has not been proven.

Since only a limited number of subjects have been treated with atacicept and these subjects have been followed for a relatively short time, the long-term side effects of taking atacicept are unknown.

Study procedures include two chest X ray exams and regular blood sampling; some minor risks are associated with these procedures.
The standard chest X-ray will involve a small radiation exposure. The radiation exposure is very low and is equal to that you would get from natural sources (like the sun) in less than 2 weeks.
Blood will be taken at each of the 21 study visits. A number of laboratory tests will be performed (depending upon the visit, tests will differ). The amounts of blood collected are unlikely to cause you any harm spread out over the period of the study. The needles used to draw blood may cause local pain, bruising and swelling. Some patients may also experience light-headedness, dizziness, occasional (but rare) fainting or local infection. For your safety, your study doctor may want you to have blood tests more frequently than your scheduled study visits. He/She will let you know if this becomes necessary.
ECG (a test to check your heart) and measurements of blood pressure, heart rate and body temperature are safe and are unlikely to cause discomfort.
In a pharmaceutical study like this one, not every risk or side effect can be predicted. Each person*s reaction to a test, drug, or procedure may be different. You may have a side effect or be at risk for symptoms, illnesses and/or complications that could not be predicted by the study doctor or the makers of atacicept.

# Contacts

**Public**
Merck BV - An affiliate of Merck Serono S.A.

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NL
**Scientific**
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NL

# Eligibility criteria

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

## Inclusion criteria

Complete lists of inclusion and exclusion criteria may be found in Section 5.2.;The trial will enrol subjects from 16 years old of either gender who have a diagnosis of SLE satisfying at least 4 of the 11 ACR criteria and a disease history of at least six months. Eligible subjects must have active SLE with at least one BILAG A or B score at screening (excluding a single B due to haematological values) requiring a change in the dose of corticosteroids, and must have a positive antinuclear antibody (ANA) test (HEp-2 ANA 1:80 and/or anti-dsDNA 30 IU/mL) at the initial screening visit.

## Exclusion criteria

Complete lists of inclusion and exclusion criteria may be found in Section 5.2.;Subjects who have active moderate to severe glomerulonephritis will be excluded, as will those who have received any treatment with rituximab, abatacept or belimumab, those who have initiated new immunosuppressive drugs or have used cyclophosphamide, calcineurin inhibitors or investigational treatments within specified periods before screening, those who have had introduction of or increases in treatment regimen of azathioprine, mycophenolate mofetil, hydroxychloroquine, chloroquine or methotrexate within 2 months before the screening visit, and those who have clinically significant abnormalities on screening laboratory tests, or who have any condition that in the Investigator*s opinion constitutes a risk or a contraindication for participation to the trial or that could interfere with the trial objectives, conduct or evaluation.
Pregnant women and breastfeeding women will also be excluded.
History of any demyelinating disease, such as MS or ON.

# 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

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-06-2008 |
| Enrollment: | 34 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Atacicept |
| Generic name: | TACI-Fc5 |

## Ethics review

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|---|---|
| Approved WMO Date: | 01-04-2008 |
| Application type: | First submission |
| Review commission: | IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam) |
| Approved WMO Date: | 09-12-2009 |
| Application type: | Amendment |
| Review commission: | IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam) |
| Approved WMO Date: | 19-03-2011 |
| Application type: | Amendment |
| Review commission: | IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam) |

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|---|---|
| Approved WMO Date: | 16-08-2011 |
| Application type: | Amendment |
| Review commission: | IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam) |

# 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 | 2007-003698-13 |
| CCMO | NL20954.003.08 |