Phase IIa, 2:2:1 randomised, double-blind, placebocontrolled, parallel group, multi-centre clinical trial to investigate the safety, efficacy and pharmacokinetics of recombinant human soluble Fc-gamma receptor IIb (SM101) for intravenous application in the treatment of systemic lupus erythematosus (SLE) patients with or without a history of lupus nephritis

Published: 21-10-2011
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The primary objective of the study is:Evaluate the safety of 6.0 mg/kg and 12 mg/kg SM101 per week in SLE patients with or without a history of lupus nephritis.The Secondary objective is:Evaluate the efficacy and pharmacokinetics (PK) of 6.0 mg/kg...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON37386

Source
ToetsingOnline

Brief title
SMILE (SM101 in Lupus Erythematosus)

Condition

- Autoimmune disorders

Synonym
Auto-immune disease, Systemic lupus erythematosus

Research involving
Human

Sponsors and support

Primary sponsor: SuppreMol GmbH
Source(s) of monetary or material Support: SuppreMol GmbH

Intervention

Keyword: Efficacy, Safety, SM101, Therapy

Outcome measures

Primary outcome

Safety parameters: Physical examination, vital signs, body temperature, body weight, electrocardiogram (ECG), safety laboratory assessments, anti-drug antibody (ADA)/neutralising anti-drug antibody (NADA), AE recording

Efficacy parameters: Overall and renal disease score assessments, proteinuria, urine sediment, GFR, biological markers, anti-dsDNA, anti-C1q, C3, C4, uNGAL, use of rescue medication

Pharmacokinetic parameters: SM101 PK: Cmax, tmax, t1/2, AUC0-t, AUC0-*, Cl, MRT, Vd and Vdss

Secondary outcome

Not Applicable

Study description

Background summary

In autoimmune diseases, such as SLE or ITP, the patient's immune system has lost the ability to discriminate between body-own (*self*) and foreign proteins. In consequence, antibodies are generated that recognise *self*-proteins and form immune complexes which continuously activate the immune system because the *self*-protein is permanently produced. This chronic condition can persist for years leading to severe organ damage and to the death of the patient. In SLE, human auto-antibodies form complexes with double-stranded DNA (dsDNA), nucleosomes, complement component 1q (C1q) and other self-structures, which are subsequently recognised by cell-bound Fc-receptors that mediate phagocytosis of these immune complexes leading to inflammation, organ damage and additional immunological activation.

The recombinant human SM101 competes for the interaction with immune complexes, thereby preventing the binding of these immune complexes to the cell. In in-vitro and in-vivo experiments it could be shown that administration of SM101 significantly inhibits antigen presenting cells and the secretion of interleukin6 (IL6) and tumour necrosis factor (TNF), which resulted in an inhibition of B-cells and reduced levels of pathogenic antibodies. As a result, the feedback loop of autoantibody production, immune complex formation and restimulation of immune cells is inhibited and, in consequence, inflammation, organ damage and additional immunological activation are prevented. At the same time, the inhibition of phagocytosis results in an increase in the concentration of circulating immune complexes which is leading to apoptosis of auto reactive B-cells that interact with these immune complexes via their high affinity B-cell receptor (Xiang et al., 2007). The elimination of auto reactive plasma cells finally leads to a new homeostasis in the immune system and subsequently to a curative effect that changes the long term prognosis of the patients.

Therapy with SM101 has the advantage of not leaving the patient immunosuppressed for long periods of time. The soluble Fc-receptor is associated with a relatively short half-life and will leave the patient with full immune competence once the therapy is halted. Furthermore, SM101 reacts specifically with immune complexed IgG and does not interfere with complement activation or IgM production. Thus, opportunistic infections during treatment with SM101 are not expected. However, the mechanism of action for SM101 is not yet fully understood.

Study objective

The primary objective of the study is:

Evaluate the safety of 6.0 mg/kg and 12 mg/kg SM101 per week in SLE patients with or without a history of lupus nephritis.

The Secondary objective is:
Evaluate the efficacy and pharmacokinetics (PK) of 6.0 mg/kg and 12 mg/kg SM101 per week in SLE patients with or without a history of lupus nephritis.

Study design

Phase IIa, 2:2:1 randomised, double-blind, placebo-controlled, parallel group, multi-centre PoC clinical trial

Intervention

Not Applicable

Study burden and risks

Risks
Until March 2011, approximately 72 patients and healthy volunteers have been treated with SM101 in 2 trials so far. SM101 appears to be generally well tolerated and safe.

However some patients may experience some adverse reactions which have been not reported so far.

As with other therapeutic proteins, administration of SM101 might cause signs of an allergic reaction to the substance. These signs could be rash, redness, itching, acute circulation disorders with decrease or increase in blood pressure, increase in cardiac frequency, dizziness, shivers, breathlessness (dyspnea), nausea or, in rare cases, an anaphylactic shock. An anaphylactic shock represents the most severe form of an allergic reaction that might lead to a collapse of the blood circulation or of the respiratory system. Immediate adequate measures will be taken if such a rare case happens. Further symptoms of an allergic reaction are, e.g.: headaches, fever, vomiting, irritations of Patient belly, joint and muscle pain, pain in general, diarrhea, skin edema or irritation of the nose's or throat's mucous membrane. Local inflammation like swellings, redness, bruises, skin hardening and itching at the injection site might also appear.

The side effects may be a minor inconvenience or could be severe enough to be life threatening or fatal. Patients will be watched closely for any side effects, and the drug will be stopped if serious side effects develop. The presence of infectious, i.e. contagious compounds in the medicinal product is most unlikely but cannot be completely excluded.

Research of the effect of SM101 on unborn babies is not available. For safety reasons, it is therefore necessary that female study participants as well as male study participants and their partners use birth control methods throughout the study. Development toxicity studies in animals revealed no adverse effect to the foetus or dam. Should the patient or their partner become pregnant during the clinical trial then the study doctor should be informed immediately.

Research on the expression of SM101 in mother milk is not available. In order to prevent unnecessary risks, the patient will undergo regular medical monitoring examinations during the trial. The study doctor will inform the patient in a detailed interview about the disorders which might appear and require immediate contacting of the study doctor. Blood sampling can lead to inflammation, pain, swelling, reddening and/or bruises (hematomas) at the sampling site.

There also may be other side effects that cannot be predicted. Other drugs will be given to make side effects less serious and uncomfortable.

Benefits
It is not known for certain that there will be any clinical benefit by taking part in the trial although we hope that the treatment will help the patient. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with systemic lupus erythematosus

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.Patient has provided written informed consent prior to any study-related procedure
2.Male or female adult patients aged 18 years or older
3.Patients with a body weight between >= 40 kg and <= 100 kg
4.At least 4 criteria of the American College of Rheumatology (ACR) revised criteria (APPENDIX 1) documented in the medical history
5.A SELENA-SLEDAI score of at least 6 within 8 weeks prior to the first IP dosing.
A subpopulation will fulfil in addition the following criteria for lupus nephritis:
a) A history of class III, IV, or a combination of these with class V glomerulonephritis, within 36 months prior to first IP dosing confirmed by a renal biopsy according to the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) [APPENDIX 2].
The patient had never a pure class V or VI glomerulonephritis
during the disease course
AND
b) Proteinuria between > 0.2 to <= 3.5 g/day at SCR
6.Patients with a present serological active status defined as abnormal laboratory values from the last 2 local serum samples for the following parameters:
a) serum antibodies against double-stranded DNA (anti-dsDNA) above upper limit of normal (ULN)
OR/AND
b) complement component 3 (C3) below lower limit of normal (LLN)
Abnormality will be confirmed by a central laboratory during screening.
7.Patients with immunosuppressant SLE treatment (if any) other than listed under 8. have completed their SLE therapy prior to first IP dosing as follows:
a) B-cell depleting agents (e.g. rituximab, epratuzumab, etc.) for >= 48 weeks
b) B-cell modifying agents (e.g. belimumab, atacicept, etc.) for >= 24 weeks
c) Intravenous immunoglobulins (IVIGs) for >= 12 weeks
d) All other immunosuppressive SLE treatment (e.g. metho-trexate, cyclophosphamide, cyclosporine, tacrolimus, etc.) for >= 8 weeks
8.Patients with a stable maintenance immunosuppressant SLE treatment (if any) within 4 weeks prior to first IP dosing consisting of:
<= 20 mg/day prednisone (or equivalent)
alone or in combination with either

a) <= 2 mg/kg/day azathioprine (AZA)
OR
b) <= 2 g/day mycophenolate mofetil (MMF) [or equivalent];9.The maintenance immunosuppressant SLE treatment is intended to remain stable during the clinical trial but at least within 4 weeks after the first IP dosing;10.Patients with a stable adjuvant maintenance SLE treatment (if any) such as antimalarias, angotensin-converting enzyme (ACE) inhibitors, non-steroid anti-inflammatory drugs (NSAIDs), cyclooxygenase inhibitors, anticoagulation- and antiplatelet agents, hormone replacement therapy, etc. within 4 weeks prior to first IP dosing. The adjuvant maintenance SLE treatment is intended to remain stable during the clinical trial but at least within 4 weeks after first IP dosing
11.Women of childbearing potential must have a negative serum pregnancy test within 3 weeks preceding the first dose of IP and a negative urine pregnancy test on study day 1
12.Both women of childbearing potential and men must use a medically acceptable method of contraception (APPENDIX 7) prior to inclusion, throughout the study, and within 12 weeks after IP discontinuation
13.Eastern Cooperative Oncology Group (ECOG) performance status <= 2, with a life expectancy of at least 9 months (APPENDIX 8)

Exclusion criteria

1.Female patients who are nursing or pregnant, who may be pregnant, or who contemplate pregnancy during the study period
2.Patients with active SLE neurological disorder documented according to the ACR SLE criteria as listed in APPENDIX 1 within 12 weeks prior to first IP dosing
3.Patients with non-lupus related renal diseases or microthrombotic disease associated with antiphospolipid syndrome
4.Patients with known active retroviral infection such as as human immunodeficiency virus (HIV), hepatitis B or C
5.Patients with other acute infections (except minor infections such as common cold) within 4 weeks prior to first IP dosing
6.Patients with a glomerular filtration rate (GFR) of < 45 mL/min/1.73 m2
7.Patients with inadequate liver function expressed as at least one of the following:
a) Aspartate aminotransferase (AST) > 3 times ULN OR
b) Alanine aminotransferase (ALT) > 3 times ULN OR
c) Serum bilirubin > 3 times ULN
8.Any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with all study procedures
9.Known hypersensitivity to any recombinant E. coli-derived product or IP excipients (Polysorbat 20, Mannitol, Sucrose)
10.Patients participating in a concurrent clinical trial or treated with another IP within 4 weeks or five terminal half-lives (whichever is longer) prior to first IP dosing
11.History of alcohol or drug abuse within the previous 5 years
12.Any condition which in the judgment of the Investigator would place the patient at undue risk or interfere with the results of the study
13.Patients with an active malignancy

14.Patients with active, serious, life-threatening diseases

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:	Will not start
Start date (anticipated):	30-11-2011
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	soluble Fc-gamma receptor IIb
Generic name:	soluble Fc-gamma receptor IIb

Ethics review

Approved WMO Date:	21-10-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-02-2012

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-07-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-023396-25-NL
CCMO	NL38259.058.11