A Phase IIIB multicentre, randomized, double*blind, double dummy study to compare the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to methotrexate.

Published: 02-06-2008
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The primary objective for this study is to demonstrate that SC injections of abatacept are non-inferior to IV infusions of abatacept .

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

Summary

ID

NL-OMON31814

Source
ToetsingOnline

Brief title
IM101-174

Condition

- Autoimmune disorders

Synonym
Rheumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: pharma industry

Intervention

Keyword: Abatacept, Methotrexate, Phase IIIB, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary analysis will assess the proportion of subjects meeting the ACR

criteria of 20% improvement (ACR 20) after 6 months (Day 169) of treatment. The

ACR 50, ACR 70 and HAQ will also be assessed.

Secondary outcome

1) Assess the proportion of subjects with ACR 50 response at month 6 (Day 169).

2) Assess the proportion of subjects with ACR 70 response at month 6 (Day 169).

3) Assess the pharmacokinetics of SC injections of abatacept.

4) Assess the immunogenicity of abatacept.

5) Assess the change in physical function as measured by the HAQ disability

index at Month 6 (Day 169).

6) Assess the proportion of subjects with a HAQ response as measured by a

reduction of

at least 0.3 unit from baseline in the HAQ disability index at Month 6 (Day 169)

7) Assess the safety and tolerability of SC injections of abatacept.

Subjects receiving SC injections of abatacept will be assessed relative to

subjects

receiving IV infusions of abatacept.

Study description

Background summary

Abatacept, a selective costimulation modulator that prevents T cell costimulation through the CD28 pathway by binding avidly to B7, is clinically effective for the treatment of rheumatoid arthritis (RA). Currently, the only route of administration for abatacept treatment to subjects with RA is by monthly intravenous (IV) infusions conducted under the supervision of a rheumatologist/physician within a clinical setting. Bristol-Myers Squibb (BMS) is evaluating self-administration of abatacept by the subcutaneous (SC) route to allow for greater flexibility and subject acceptance. For this reason, BMS has developed a new ready-to-use formulation for SC administration.

Study objective

The primary objective for this study is to demonstrate that SC injections of abatacept are non-inferior to IV infusions of abatacept .

Study design

The study consists of a six month randomized, double-blind, double-dummy placebo-controlled treatment period followed by an open-label long term extension period (LT). The LT will continue until the SC formulation is licensed in a country or the sponsor decides to terminate the trial. During the double-blind period, all subjects will receive abatacept; through two different routes of administration. One group (520 subjects) will receive weekly SC injections of abatacept and another group (260 subjects) will receive monthly IV infusions of abatacept. A *double-dummy* design will be used to protect the blind. Thus, subjects receiving IV infusions of abatacept (*Abatacept IV*) will also receive SC injections of placebo (*Placebo SC*). Conversely, subjects receiving SC injections of abatacept (*Abatacept SC*) will also receive IV infusions of placebo (*Placebo IV*). On Day 1 a loading dose of Abatacept IV will replace the Placebo IV treatment. After 6 months, all subjects will enter the LT during which all subjects will receive weekly Abatacept SC. Subjects will not receive any IV infusions (active or placebo) in the LT.

Intervention

SC abatacept is the investigated product in this study. Abatacept SC will be administered at a weekly dose of 125 mg (1 mL). All subjects randomized to Abatacept SC will also receive a loading dose of Abatacept IV on Day 1 based on their body weight as described below.

Abatacept IV dosage will be stratified on body weight as follows: 500 mg for subjects weighing < 60 kg, 750 mg for subjects weighing 60 to 100 kg and 1 gram for subjects weighing > 100 kg. Abatacept IV will be administered on Days 1, 15, 29 and every 28 days thereafter for the first six months of the study in subjects assigned to Abatacept IV. All randomized subjects will receive placebo in the first 6 months of the study in addition to the abatacept treatment to maintain the blind. Subjects randomized to Abatacept SC will receive monthly IV infusions of placebo, while subjects randomized to Abatacept IV will receive weekly SC injections of placebo.

Study burden and risks

Burden: physical exams, a maximum of 10 hospital visits in the short term part of the study, monthly phone calls and quarterly hospital*s visits in the long term part of the study, 1 chest x-ray, 1 PPD test, yearly breast examinations, breast screening procedures according to local regulations, monthly blood sampling, monthly intravenous infusions, weekly subcutaneous injections, weekly completion of a diary card, joint counts at each visit, global assessment of disease activity by subject and physician at each visit, subject assessment of physical function (HAQ) at each visit, urine and pregnancy testing monthly.
Risks: possible adverse events of abatacept.
Benefit: treatment of RA. In the long term portion of the study subjects may also benefit from the convenient use of the weekly self administration of abatacept injection by a subcutaneous route in comparison to the monthly IV infusions.
Group relatedness: knowledge gain from this study may also help other patients in the future.

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) Signed Written Informed Consent
2) Subjects must meet the criteria of the American Rheumatism Association (1987) for the diagnosis of rheumatoid arthritis and the American College of Rheumatology (1991) functional Classes I, II, or III. (protocol appendices 3 and 4).
c) Subjects with stable renal, endocrine, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological or cerebral disease(s) (eg, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease) will be allowed to participate in this study.
d) Subjects who are considered methotrexate inadequate responders by a treating physician or investigator. Subjects must have been taking methotrexate for at least 3 months at a minimal weekly dose of 15 mg, and at a stable dose for 28 days prior to randomization.
a) Men and women, ages >= 18
Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study for 4 weeks before and for up to 10 weeks after the last dose of abatacept in such a manner that the risk of pregnancy is minimized.
4) Oral corticosteriod treatment must have been reduced to the equivalent of <= 10 mg prednisone daily for 28 days and stabilized for at least 25 out of 28 days prior to treatment (Day 1). No intra-articular or IM injections of corticosteriods are permitted within 28 days prior to treatment (Day 1).
5) At randomization, subjects receiving methotrexate monotherapy must have the following disease activity at randomization:
i) 10 or more swollen joints (66 joint count) and

ii) 12 or more tender joints (68 joint count) and
iii) C reactive protein (hsCRP) >= 0.8 mg/dL (result used from screening visit).
b) For subjects receiving methotrexate plus other DMARDs/Biologics (requiring washout):
At screening visit, subjects must have the following disease activity:
i) 6 or more swollen joints (66 joint count) and
ii) 8 or more tender joints (68 joint count) and
iii) no restriction on hsCRP
After washout, at randomization (Day 1), subjects must have the following disease activity:
i) 10 or more swollen joints (66 joint count) and
ii) 12 or more tender joints (68 joint count) and
iii) Creactive protein (hsCRP) >= 0.8 mg/dL (result used from screening or Day -3 visit).
6) Subjects must be willing to self-inject or allow a caregiver to do it for them.
7) Subjects must be able to adhere to the study visit schedule, understand, and comply with other protocol requirements.

Exclusion criteria

1) Sex and Reproductive Status
a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period b) Women who are pregnant or breastfeeding. c) Women with a positive pregnancy test on enrolment or prior to investigational product administration;2) Target Disease Exceptions
a) Subjects who meet diagnostic criteria for any other rheumatic disease (eg, lupus erythematous).
b) Subjects with active vasculitis of a major organ system (except for subcutaneous rheumatoid nodules).;3) Medical History and Concurrent Diseases
b) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological, or cerebral disease. Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
c) Female subjects who have had a breast cancer screening study that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations (please refer to Section 6.3.6).
d) Subjects with a history of cancer within the last five years (other than nonmelanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing. Subjects with carcinoma in situ, treated with definitive surgical intervention prior to study entry, are allowed.
e) Subjects who have clinically significant drug or alcohol abuse.
f) Subjects with any serious acute bacterial infection (such as pneumonia or pyelonephritis unless treated and completely resolved with antibiotics).
g) Subjects with severe chronic or recurrent bacterial infections (such as recurrent pneumonia, chronic bronchiectasis).
h) Subjects at risk for tuberculosis (TB). Specifically, subjects with:
i) Current clinical, radiographic or laboratory evidence of active or latent TB.

ii) A history of active TB within the last 3 years even if it was treated.
iii) A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type.
i) Subjects with herpes zoster that resolved less than 2 months prior to enrolment.
j) Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrolment, including subjects with evidence of Human Immunodeficiency Virus (HIV) infection
4) Physical and Laboratory Test Findings
a) Hepatitis B surface antigen-positive subjects.
b) Hepatitis C antibody-positive subjects who are also RIBA-positive or PCR positive.
c) Subjects with any of the following laboratory values:
i) Hgb < 8.5 g/dL.
ii) WBC < 3,000/mm3 (3 x 109/L)
iii)Platelets < 100,000/mm3 (100 x 109/L).
iv) Serum creatinine > 2 times upper limit of normal.
v) Serum ALT or AST > 2 times upper limit of normal.
vi) Any other laboratory test results that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
6) Prohibited Treatments and/or Therapies
a) Subjects who have received treatment with rituximab.
b) Subjects who have had prior exposure to abatacept (Ctla4-Ig)
c) Subjects who have been exposed to any investigational drug or placebo or approved biological agent within 4 weeks or 5 half-lives, whichever is longer, or within 3 months for any biological agent with an unknown half-life.
d) Subjects currently (or in the last 3 months) receiving treatment with azathioprine, gold, leflunomide, immunoadsorption columns (such as Prosorba columns), mycophenylate mofetil (CellCept®), cyclosporin A, other calcineurin inhibitors or D-Penicillamine.
e) Subjects who have received any live vaccines within 3 months of study drug administration or are scheduled to receive live vaccines.
7) Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated.
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2008
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orencia
Generic name:	Abatacept
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-06-2008
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	16-07-2008
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	19-11-2008
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	01-12-2008

Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-01-2009
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	18-03-2009
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	13-07-2009
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	03-03-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	06-09-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Approved WMO Date:	10-12-2013
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2007-005434-37-NL
ClinicalTrials.gov	NCT00547521
CCMO	NL21140.099.08