A Phase 3B, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Abatacept SC in Combination with Methotrexate Compared to Methotrexate Monotherapy in Achieving Clinical Remission in Adults with Early Rheumatoid Arthritis who are Methotrexate Naive

Published: 10-12-2015
Last updated: 19-04-2024

Primary ObjectiveThe primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with methotrexate to methotrexate alone in achieving Remission, defined as SDAI less than or equal to 3, at Week 24....

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

Summary

ID

NL-OMON43711

Source
ToetsingOnline

Brief title
IM101-550

Condition

- Autoimmune disorders

Synonym
Rheumatoid Arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Abatacept, Methotrexate, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary efficacy endpoint is the proportion of subjects in SDAI Remission

at Week 24.

Secondary outcome

The secondary endpoints below will be assessed in the order below in a

hierarchical fashion after the primary endpoint is met to preserve the type I

error of the study at 5%

(1) Proportion of subjects in DA28-CRP Remission at Week 24

(2) Proportion of subjects in SDAI Remission at Week 52

(3) Mean change from baseline in TSS at Week 52

(4) Proportion of subjects in Boolean Remission at Week 52

Study description

Background summary

Achieving remission in patients with rheumatoid arthritis has become an

important goal in the treatment of rheumatoid arthritis. This is because it has been shown that improving the disease as early as possible after diagnosis can result in less long term and irreversible damage to joints and physical disability. Taking control of disease activity and reducing it as early as possible is the current target approach. It has become important to evaluate new and current rheumatoid arthritis therapies to see how the prevention of the progression of this disease can be attained. Until recently, there has been no defined standard of care for early stage rheumatoid arthritis other than symptomatic treatment with NSAIDs and corticosteroids before starting conventional DMARD therapy.

It is understood that there may be a *window of opportunity* for the effective treatment of recently diagnosed rheumatoid arthritis patients, and this was demonstrated in patients whom received early DMARD treatment had better outcomes in regards to physical ability and ability to work than those in whom therapy was delayed even by a few months. Based on current knowledge, patients with early rheumatoid arthritis that are treated with abatacept, would be expected to have a high chance of achieving an improvement in their disease.

The aim of this study is to determine if treatment with abatacept in combination with methotrexate will achieve a higher rate of remission versus methotrexate alone in adults, that have not yet been treated with methotrexate.

The first phase of the study (Induction Period) is designed to compare the rate of disease improvement using some strict criteria.

There has also been an interest in decreasing or withdrawing treatment as a patient improves. Retreatment would only be started again as necessary. This is the aim of the second phase of the study called the De-escalation Period.

Study objective

Primary Objective
The primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with methotrexate to methotrexate alone in achieving Remission, defined as SDAI less than or equal to 3, at Week 24.

Secondary Objectives
1) To compare the efficacy of weekly abatacept + methotrexate to methotrexate alone in achieving remission by DAS28 CRP Remission criteria at Week 24.
2) To compare the efficacy of weekly abatacept + methotrexate to methotrexate alone in achieving remission by SDAI remission criteria at Week 52.
3) To compare the efficacy of weekly abatacept + methotrexate to methotrexate alone in reducing joint damage by X-ray at Week 52.
4) To compare the efficacy of weekly abatacept + methotrexate to methotrexate alone in achieving remission by Boolean remission criteria at Week 52.

Study design

This study is a phase 3, randomised, double-blind study which will be separated into 2 phases. Firstly, an Induction Period, which will last for 56 weeks, and treatment will be self-administered on a weekly basis. Patients will be required to attend for hospital visits on a monthly basis. The second phase is the De-escalation Period which will last for 48 weeks, and treatment will be self-administered. Patients will be required to attend for hospital visits on a monthly basis. Patients will be allowed to escape to open-label treatment at specific time points during the study if they are not responding. A follow up visit is required.

Intervention

In this study, investigational products are abatacept subcutaneous 125mg in 1 ml pre-filled syringes and oral methotrexate tablets and capsules at 2.5mg. Placebo will given depending on what treatment the patient is randomised to.

In the Induction Period, all patients will be randomly assigned to one of two treatment arms:
Arm A: Combination treatment: Active abatacept plus methotrexate weekly
Arm B: Methotrexate monotherapy (standard of care): Placebo abatacept plus methotrexate weekly

Patients who achieve remission will be re-randomised to one of four treatment arms in the De-escalation Period. To maintain the double-blind, a double-dummy regimen will be used.

Patients who were assigned to a combination treatment during the Induction Period have an equal chance of getting one of the following treatments in the De-escalation Period:

1) Continue active abatacept weekly plus methotrexate weekly for 12 months
2) Reduce active abatacept to every other week plus methotrexate weekly for 6 months then reduce further to placebo abatacept weekly plus methotrexate weekly for 6 months
3) Continue active abatacept weekly + convert to placebo methotrexate for 12 months

Patients who were assigned to methotrexate alone during the Induction Period will continue to receive methotrexate alone for 12 months.

Study burden and risks

Burden: study procedures (physical examination, blood sampling, completing questionnaires and diary, and regular pregnancy testing for women) and regular

attendance for hospital visits on a monthly basis. The patient will also be required to have x-rays and self-administer weekly subcutaneous and oral treatment themselves (or by a caregiver).

Risks: Abatacept was first approved in 2005. Post-marketing reports have not altered the favourable benefit-risk profile for abatacept and its safety profile remains generally similar to that established during the clinical trials. Abatacept treatment in rheumatoid arthritis has an acceptable safety profile regarding serious infections, malignancies and autoimmune reactions that are usually a concern with agents acting on the immune system. The main identified risks of abatacept therapy are infections (primarily bacterial), autoimmune events (primarily psoriasis), and slightly increased risk of infusion reactions versus placebo. The overall frequency of infections was slightly increased in the abatacept treated population, but the severity, treatment, and outcome of these infections was similar to those treated with placebo. Serious viral, fungal, or mycobacterial infections were uncommon. In order to minimise the overall risk to participating patients, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments, exclusionary screening tests (chest x-ray, tuberculosis screening, medical history), and specific follow-up safety assessments.

Benefit: Abatacept has demonstrated consistent and statistically robust effects on all primary and secondary endpoints in Bristol-Myers Squibb rheumatoid arthritis efficacy trials. Based on the data from three previous studies, the use of abatacept (in combination with methotrexate) in early rheumatoid arthritis has the potential to induce remission in a large proportion of patients that is then sustained for months after cessation of biologic and non-biologic DMARDs. The ability to sustain remission for a period of time after stopping DMARDs would have the additional benefit of limiting exposure to immunosuppressants. Finally, very early use of effective therapy may curtail or even halt radiographic progression of disease which could lead to long-term joint protection.

Group relatedness: knowledge gain from this study may also help other patients in the future.

Contacts

Public
Bristol-Myers Squibb

Orteliuslaan 1000
Urecht 3528 BD
NL

Scientific
Bristol-Myers Squibb

Orteliuslaan 1000
Urecht 3528 BD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects that have early RA as defined as:
- Diagnosis made by the ACR/EULAR 2010 criteria for the classification of RA
- Diagnosis made within the past 6 months;2. Subjects must meet at least one of the following criteria:
- CRP greater than 0.3 mg/dL (ULN)
- ESR greater than or equal to 28 mm/h;3. Subjects that have at least 3 tender joints and at least 3 swollen joints using the 28 Joint Count Assessment at both screening and Day 1;4. Subjects are positive for anti-citrullinated protein antibodies (ACPA);5. Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of less than or equal to 10 mg prednisone daily for at least 4 weeks.;6. Men and women aged more than 18 years old;7. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug; must not be breastfeeding; agree to follow instructions for methods of contraception for the duration of treatment with study drug plus a total of 100 days post-treatment completion.;8. Men who are sexually active with WOCBP must agree to follow instructions for methods of contraception for the duration of treatment with study drug plus 160 days post-treatment completion.;9. At a minimum, subjects must agree to use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in the protocol.

Exclusion criteria

1. Target Disease Exceptions
a) Subjects with autoimmune disease other than RA (eg, SLE, Juvenile Idiopathic Arthritis, vasculitis, seronegative spondyloarthritis, Inflammatory Bowel Disease). However, subjects with secondary Sjogren*s syndrome will be allowed.
b) Prior history of or current inflammatory joint disease other than RA (such as, systemic lupus erythematosus, gout, reactive arthritis, Lyme disease)
c) Subjects with active fibromyalgia
d) Subjects who have a history of Felty*s Syndrome;2. Medical History and Concurrent Diseases
a) Subjects at risk for tuberculosis (TB) defined as follows:
i) Current clinical, radiographic or laboratory evidence of active TB. Chest x-rays (PA and lateral) obtained within the 6 months prior to randomisation will be permitted. TB testing (interferon gamma release assay or PPD) performed in the past month prior to randomisation will be accepted.
ii) A history of active TB unless there is documentation that the subject had received prior anti-TB treatment that was appropriate in duration and type.
iii) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they have no evidence of current TB on chest x-ray at screening and they are actively being treated for TB with isoniazid (INH) or other therapy for latent TB given according to local health authority guidelines. If permitted by local guidelines regarding treatment with biologic medications, subjects may be randomised prior to completion of treatment as long as they have completed at least 4 weeks of treatment and they have no evidence of current TB on chest x-ray at screening.;b) Subjects with recent acute infection defined as:
i) Any acute infection within 60 days prior to randomisation that required hospitalisation or treatment with parenteral antibiotics
ii) Any acute infection within 30 days prior to randomisation that required oral antimicrobial or antiviral therapy;c) Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis) or serious latent viral infections at the time of enrollment, including subjects with evidence of Immunodeficiency Virus (HIV) infection.;d) Subjects with any history of infection of a joint prosthesis or artificial joint.;e) Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiomycosis);f) Subjects with history of recurrent herpes zoster (more than 1 episode) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex, or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to screening;g) Subjects with history of primary or secondary immunodeficiency or a family history of a
primary immune deficiency in a first degree relative.;h) Subjects who have present or previous malignancies, except documented history of cured non-metastatic squamous or basal skin cell carcinoma, or cervical carcinoma in situ, with no recurrence in the 5 years prior to screening. Subjects who had screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations;i) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary,

psychiatric, cardiac, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections. ;j) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Subjects who are in close contact with others who have received a live vaccine may be enrolled at the investigator*s discretion.;k) Subjects who have undergone a major surgical procedure within the 60 days prior to randomisation.;l) Subjects for whom 5 or more joints cannot be assessed for tenderness or swelling (e.g, due to surgery, fusion, amputation, etc).;m) Subjects with a history of (within 12 months of signing informed consent), or known current problems with drug or alcohol abuse history or known cirrhosis including alcoholic cirrhosis;n) Subjects who are impaired, incapacitated, or incapable of completing study related
assessments.;3. Physical and Laboratory Test Findings
a) Hepatitis B surface antigen (HBsAg)-positive, or Hepatitis B core antibody (HBcAb) positive subjects with detectable hepatitis B viral DNA
b) Hepatitis C antibody (HcAb)-positive subjects with detectable hepatitis C viral RNA
c) Hemoglobin (Hgb) < 8.5 g/dl
d) White Blood Count (WBC) < 3,000/mm3 (3 x 109/L)
e) Platelets < 100,000/mm3 (100 x 109/L)
f) Serum creatinine > 2 times upper limit of normal
g) Serum ALT or AST > 2 times upper limit of normal;4. Allergies and Adverse Drug Reaction
a) Hypersensitivity to one of the investigational product excipients;5. Prohibited Therapies:
a) Subjects who have had prior exposure to abatacept (CTLA4-Ig)
b) Subjects who have been exposed to any treatment with an approved or investigational conventional (non-biologic) or biologic DMARD including but not limited to methotrexate, sulfasalazine, leflunomide, hydroxychloroquine/chloroquine, calcineurin inhibitors, tofacitinib, infliximab, etanercept, anakinra, adalimumab, rituximab, tocilizumab, golimumab, and certolizumab
c) Subjects who have received an IM, IV, or IA administration of a corticosteroid * 6 weeks prior to randomisation
d) If subjects are taking NSAIDs the dose must be stable, as assessed by the Investigator, for 14 days prior to randomisation

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:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	24
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	10-12-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	08-06-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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	EUCTR2015-001275-50-NL
ClinicalTrials.gov	NCT02504268
CCMO	NL54040.058.15