A randomized double blind-placebo controlled dose ranging study to evaluate the efficacy and safety of SAR153191 in patients with Ankylosing Spondylitis (AS)

Published: 15-12-2009
Last updated: 04-05-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON34801

Source
ToetsingOnline

Brief title
ALIGN

Condition

- Central nervous system infections and inflammations

Synonym
Bechterew's disease, Marie Strümpell disease

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Ankylosing Spondylitis, Anti-IL-6R mAb, Interleukine 6

Outcome measures

Primary outcome

The primary objective of the study is to evaluate the efficacy by (ASAS20)

(Assessment in Ankylosing Spondylitis Working Group responses criteria) of

SAR153191 in patients with AS (Ankylosing Spondylitis) at week 12 and to define

the best dose/dosage regimen for further

development.

Secondary outcome

The secondary objectives are:

* assessment of higher level of response ASAS40;

* ASAS partial remission;

* disease activity (BASDAI) at Week 12;

* range of motion assessed by (BASMI) (10-point scale);

* Ankylosing Spondylitis Disease Activity Score (ASDAS);

* safety and tolerability of SAR153191 in patients with AS;

* and to document PK profile of SAR153191 in patients with AS;

* MRI of the spine.

Study description

Background summary

Ankylosing Spondylitis (AS) is a chronic, progressive inflammatory disease characterized by inflammatory back pain, due to sacroiliitis, spondylitis and enthesitis that affects young men and women, commonly starting in the second and third decades of life. Traditional therapies
for AS are nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and physical therapy. However the above mentioned therapies have limited efficacy. In contrast, the anti-Tumor Necrosis Factor (anti-TNF) agents have shown better clinical efficacy in short and intermediate * term evaluations, but 30% to 40% of patients are still anti-TNF resistant (patients with no improvement in pain or function) (1)(2)(3). Patients who do not respond to anti-TNF may be less responsive to other biological treatments. Despite the medical therapies some patients still require surgical intervention after failure of other treatments modalities.
Interleukin-6 (IL-6) is an important cytokine for the pathogenesis of AS. It is mostly secreted by mononuclear phagocytes and activated Th cells. Its function is to maintain growth and differentiation of B cells and the production of immunoglobulins. There is evidence that the inflammation in AS is at least partly mediated by tumor necrosis factor-alpha and IL-6, as high levels of these cytokines have been found in biopsy from sacroiliac joints of patients with AS. Also high levels of circulating IL-6 have been found in several groups of AS patients. However, no IL-6 mAb has been approved in this indication.

Study objective

The purpose of this study is to determine if SAR153191 SC (subcutaneous) injection once a week or every other week is safe and effective compared to placebo (an inactive solution injection) in reducing the recurrence and symptoms of Ankylosing Spondylitis. This is a specific condition you have.

Study design

This is a multi-center, multinational study. The design is a double-blind, randomized parallel group placebo-controlled, 12 weeks study treatment of up to 6 arms (5 active dose regimens) or placebo. Patients with active AS will be randomized in a ratio 1:1:1:1:1:1 (SAR153191:
placebo) with screening hs-CRP (hs-CRP *1.5 mg/L or >1.5 mg/L) and region as stratification factors.
Patients will receive one of the 5 SAR153191 dose regimens (SAR153191 weekly or SAR153191 every other week alternating with placebo every other week) or placebo weekly for 12 weeks of treatment.

Intervention

SAR153191 the anti-human IL-6R* antibody is a fully human monoclonal antibody which will be administered subcutaneous one a week. The following doses are selected:
- Arm 1: 100 mg SAR153191 once a week;
- Arm 2: 150 mg SAR153191 once a week;
- Arm 3: 100 mg SAR153191 every other week, alternating with placebo every other week;
- Arm 4: 150 mg SAR153191 every other week, alternating with placebo every other week;
- Arm 5: 200 mg SAR153191 every other week, alternating with placebo every other week;
- Arm 6: placebo once a week.

This study comprises of 3 periods:
* Screening period (approximately 2 weeks):
* Treatment period (12 weeks):
* Post-treatment follow-up period (approximately 6 weeks from last drug injection):
If the patient fullfills the treatment period completely, he or she can participate in an extension study with open label SAR153191. This study will start after 12 weeks of treatment. And the follow-up period will be declined.

Study burden and risks

De patient visits the hospital for a minimum of 7 visits and a maximum of 9 visits during the study. The first visit is the screening visit, which is followed by a randomization visit (Day 1), a visit at week 2, 4, 8, 12 and 18. The patient can take the opportunity to be visited at home by a home nursing service at week 6 and 10. This is arranged by the sponsor. If the patient is more comfortable to visit the hospital, then this is not a problem. During these (hospital) visits bloodsamples will be taken, an ECG will be made, a MRI and X-rays will be performed and several questionnaires have to be completed. Further at the beginning of the study it will be checked if the patient does not have Tuberculosis and/or Hepatitis B of C.

Bloodsamples
During blood draws, the patient may have pain and/or bruising at the place on the arm where blood is taken. Blood clots may form and infections may occur, but these events are rare. The amount of blood to be drawn will be approximately 250 mL over 20 weeks.

Study medication
Treatment with SAR153191 may increase the risk of infection including tuberculosis (TB), due to the fact that the immune system may become weaker and

not able to fight infections as it should therefore causing bacteria, fungi, or viruses to spread throughout thebody. It is possible that the body may develop antibodies (proteins that your body makes when exposed to foreign substances) to this new drug.
The patient may suffer from bruises, pain or discomfort at injection or puncture sites.

ECG, MRI and X-ray
There might only be a little discomfort, but not risk, when the electrocardiogram electrodes are placed on the skin and the recording of the electrocardiogram.
During the MRI the patient need not to move or change his/her position; and this may be uncomfortable due to the AS.
Radiation exposure from an X-ray of the spine is equivalent to the amount of radiation exposure one experiences from 6 months of natural sunlight. Radiation exposure from a Chest X-ray is equivalent to the amount of radiation exposure from 10 days of natural sunlight.

Pregnancy
If the patient has childbearing potential, she must either have been surgically sterilised (tuballigation or hysterectomy) at least one month prior to study entry or use an IUD (intrauterine device) combined with diaphragm, condom or spermicide, or use an oral contraceptive (the pill) together with a barrier method, in any case she must have a negative pregnancy test at the baseline visit. and every 4 weeks during the study.

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

* Male and Female *18 years old and <75 years old with the diagnosis AS according to the modified New York criteria.
* Patient must had an adequate trial of at least 2 different Non Steroidal Anti-Inflammatory Drugs (NSAIDs), taken for at least 2 weeks in each case and on a stable dose for *2 weeks or be intolerant to NSAIDs
* Patients must have active AS for *3 months before screening and active disease must be present at screening and at baseline
* Active AS is defined by:
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of *4 Numerical Rating Scale
(NRS 0-10)
- Total back pain score *4 (NRS 0-10)
* Patients treated with corticosteroid must be on a stable dose for *2 weeks prior to baseline
* Patients treated with Disease Modifying Anti-Rheumatic Drugs (DMARDs): hydroxychloroquine, sulfasalazine and methotrexate (MTX); must be on stable dose *12 weeks prior to baseline

Exclusion criteria

* Patients <18 years old and *75 years old
* Patients with complete fusion of the spine
* Past history of non response to any anti-Tumor Necrosis Factors (TNFs) treatment or non response to any other biological treatment for AS.
* Any past or current treatment with anti-TNF agents or any biological agent within 3 months prior to screening.
* Patients treated with DMARDs except for hydroxychloroquine, sulfasalazine and MTX
* MTX >25 mg/week

* Hydroxychloroquine >400 mg/day
* Sulfasalazine >3 g/day
* Treatment with oral prednisone or equivalent corticosteroids >10 mg/day within 6 weeks prior to screening
* Use of intramuscular or intra-articular corticosteroids within the last 4 weeks before screening
* Patients who had previously been treated with cyclosporine or azathioprine

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:	Pending
Start date (anticipated):	15-02-2010
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet beschikbaar
Generic name:	SAR153191

Ethics review

Approved WMO

Date:	15-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-016068-35-NL
CCMO	NL30216.018.09
Other	Zie sectie J