A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy

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Part A:To demonstrate that SAR153191 on top of MTX is effective on reduction of signs and symptoms of rheumatoid arthritis at 12 weeksPart B:• To demonstrate that SAR153191 on top of MTX is effective on reduction of signs and symptoms of RA at 24…

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

Summary

ID

NL-OMON34750

Source
ToetsingOnline

Brief title
MOBILITY

Condition

- Autoimmune disorders

Synonym
arthritis, RA

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anti- Interleukin 6R monoclonal antibody, rheumatoid arthritis

Outcome measures

Primary outcome

The primary objective in Part A is to demonstrate that SAR153191 on top of MTX

is effective on reduction of signs and symptoms of rheumatoid arthritis at 12

weeks and to define the best dose/dosage regimen for further development.

The primary objective in Part B is to demonstrate that SAR153191 on top of MTX

is effective on reduction of signs and symptoms of rheumatoid arthritis at 24

weeks.

Secondary outcome

The main secondary objectives are:

• To demonstrate that SAR153191 on top of MTX is effective on:

- inhibition of progression of structural damage at 52 weeks

- improvement in physical function at 52 weeks

- induction of a major clinical response at 52 weeks

• To assess the safety of SAR153191 on top of MTX

• To document the PK profile of SAR153191on top of MTX, in patients with active

rheumatoid arthritis who are inadequate responders to MTX therapy.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disease, primarily targeting the synovial membrane of diarthrodial joints. This process can result in progressive joint destruction, chronic disability and shortened life expectancy. Interleukin-6 (IL-6) is a key
cytokine involved in the pathogenesis of RA causing inflammation and joint destruction (1). Inhibition of IL-6 signaling through blockade of the IL-6 receptor (IL-6R) is an effective new therapeutic modality for RA as demonstrated by Tocilizumab, a humanized monoclonal antibody
to IL-6 receptor, approved in Europe in January 2009 for treatment of RA and currently under review by the FDA.
SAR153191 is administered subcutaneously, which provides the advantage over Tocilizumab, intravenous, of a self administration option which is generally more convenient. It is expected than a human mAb will provide less immunologic reactions compared to a humanized mAb.

Study objective

Part A:
To demonstrate that SAR153191 on top of MTX is effective on reduction of signs and symptoms of rheumatoid arthritis at 12 weeks
Part B:
• To demonstrate that SAR153191 on top of MTX is effective on reduction of signs and symptoms of RA at 24 weeks

Study design

This study is a worldwide, double-blind, placebo controlled, randomized study in patients with rheumatoid arthritis with an inadequate response to MTX. It will include 2 parts using an operationally seamless design.
The first part (Part A) of the study is a 12 week, 6-arm dose ranging part intended to select the 2 best dose regimens based on efficacy (reduction in signs and symptoms) and safety.

The second part (Part B) of the study is a 52 week part to confirm the efficacy and safety of these 2 selected dose regimens on reduction in signs and symptoms, inhibition of progression of structural damage, improvement in physical function and induction of major clinical response.
The operationally seamless design nature of this study resides in the fact that Part B is starting to enrol patients just after the last patient is randomized in Part A without waiting for the dose selection based on its results. Thus part B patients belong to two distinct cohorts according to the time of their enrolment:
• Cohort 1 of patients randomized before the dose selection: these patients are randomized into 6-arm (as the ones of Part A). After dose selection, the patients randomized in the 2 selected doses and the placebo regimens continue the 52-week trial but the ones
randomized in the 3 other arms are discontinued from the present study but proposed to join an open label extension (see LTS11210). Not conducted in the Netherlands.
• Cohort 2 of patients randomized after the dose selection: these patients are randomized into 3-arm, the 2 selected ones and placebo.

In summary, this operationally seamless design is using a learning stage (Part A) to select the relevant dose regimens and a confirmatory stage (Part B) to test the selected dose regimens, without interruption of inclusions but ensuring complete protection of the blindness of the trial. This proposed design is consistent with regulatory agencies initiatives (2006 Conference on adaptive trial design FDA, 2009 EMEA workshop) to streamline and improve drug development processes. The design of this study has been discussed and agreed both by the FDA and the EMEA.

Intervention

Screening phase: 4 weeks
Dubble-blind treatment phase part A: Max. 12 weeks, weekly injection with SAR153191 or placebo
Dubble-blind treatment phase part B: Max. 52 weeks, weekly injection with SAR153191 or placebo

Study burden and risks

Risks are related to blood sampling and possible side effect of the (administration of) the study drug. The burden for the patient will be the number of visits to the center as part of the trial. In addition, the patient is asked to fill in a diary.

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

• Diagnosis of rheumatoid arthritis >= 3 months duration
• Active disease defined as:
- at least 8/68 tender joints and 6/66 swollen joints
- hs-CRP >10mg/l
- Continuous treatment with MTX for at least 12 weeks prior to baseline and on stable dose (10mg/w-25mg/w) for 6 weeks prior to screening.
• Part B only:
- Bone erosion based on documented X-ray prior to first study drug dosing
- Or Cyclic Citrullinated Peptide CCP positive
- Or Rheumatoid Factor (RF) positive.

Exclusion criteria

• Age <18 years or >75 years,
• Treatment with DMARDs (other than MTX) within 4 weeks or 12 weeks prior to screening (depending on DMARDs).
• Past history of non response to prior TNF or biologic treatment,
• Any past or current biologic agents for the treatment of RA within 3 months,
• Use of parenteral glucocorticoids or intraarticular glucocorticoids within 4 weeks prior to screening visit
• Use of oral glucocorticoid greater than 10mg/day or equivalent/day, or a change in dosage within 4 weeks prior to baseline visit.

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

Recruitment status:	Will not start
Enrollment:	19
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Folic Acid
Generic name:	Folic Acid
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Methotrexate (MTX)
Generic name:	Methotrexate (MTX)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet beschikbaar
Generic name:	SAR153191

Ethics review

Approved WMO Date:	20-05-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-11-2010
Application type:	First submission
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	EUCTR2009-016266-90-NL
CCMO	NL31838.058.10
Other	Zie sectie J.