A Phase IIa Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of JNJ-38518168 in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy With Synovial Biopsy Substudy

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Primary Objective* To assess the safety, tolerability, and efficacy (in terms of change in DAS28 [using C-ReactiveProtein (CRP)] from baseline) of JNJ-38518168 at a dose of 100 mg/day for up to 12 weekscompared to placebo in subjects with active...

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

Summary

ID

NL-OMON33287

Source
ToetsingOnline

Brief title
38518168 ARA 2001

Condition

- Autoimmune disorders

Synonym
rheuma

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: De sponsor of opdrachtgever: Jansen Cilag International NV

Intervention

Keyword: JNJ-38518168, Rheumatoid Arthritis

Outcome measures

Primary outcome

STUDY ENDPOINTS

Primary

* Change from baseline in DAS28 (using CRP) score at Week 12

Secondary outcome

Secondary

* Change from baseline in DAS28 (using CRP) score at Week 12 based on

randomized subjects

who do not participate in the synovial biopsy substudy

* Change from baseline in DAS28 (using CRP) score at Week 12 based on subjects

whose MTX dose remains unchanged

* DAS28 (using CRP) response rates at Week 12

* DAS28 (using ESR) response rates at Week 12

* Change from baseline in DAS28 (using ESR) at Week 12

* ACR20/50/70/90 response rates at Week 12

* ACR20/50/70/90 response rates at Week 12 based on randomized subjects who do

not participate in the synovial biopsy substudy

* ACR20/50/70/90 response rates at Week 12 based on randomized subjects whose

MTX dose

remains unchanged

* ACR-N Index of Improvement at Week 12

* Change from baseline in CRP levels at Week 12

* Change from baseline in ESR levels at Week 12

* Change from baseline in Disability Index of the Health Assessment

Questionnaire (HAQ-DI) at

Week 12

* Change from baseline in Patient*s Global Assessment of Pain at Week 12

* Change from baseline in Physician*s Global Assessment of Disease Activity at

Week 12

* Change from baseline in Patient*s Global Assessment of Disease Activity at

Week 12

Exploratory Endpoints:

* Changes from baseline in various synovial and blood biomarkers at Week 12

Study description

Background summary

JNJ-38518168 is a potent antagonist of the histamine H4 receptor (H4R) with a Ki of 8.4 nM and greater than 25-fold selectivity over other histamine receptors. It inhibited histamine-induced shape change of eosinophils, chemotaxis of mast cells, and IL-6 production in mast cells. The compound inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor alpha (TNF-*) production in vivo. JNJ-38518168 reduced arthritic edema and joint damage in a

collagen-induced mouse model of arthritis. Based on these preclinical data, JNJ-38518168 may provide benefit to subjects with rheumatoid arthritis.

Hypothesis
* It is hypothesized that the mean improvement in DAS28 (using CRP) scores from baseline will be superior to placebo at Week 12 when JNJ-38518168 is administered to patients with active
rheumatoid arthritis despite methotrexate therapy.

Study objective

Primary Objective
* To assess the safety, tolerability, and efficacy (in terms of change in DAS28 [using C-Reactive
Protein (CRP)] from baseline) of JNJ-38518168 at a dose of 100 mg/day for up to 12 weeks
compared to placebo in subjects with active Rheumatoid Arthritis (RA) despite methotrexate
(MTX) therapy.

Secondary Objective
* To assess the efficacy of JNJ-38518168 as measured by ACR 20, 50, 70, 90 response rates at Week 12 and other efficacy assessments.

Exploratory Objectives
* To assess the effect of JNJ-38518168 on various biomarkers detected in synovial biopsy tissue and blood samples
* To characterize the population pharmacokinetics (PK) of JNJ-38518168 in adults with active
rheumatoid arthritis despite methotrexate therapy

Study design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study. Approximately 90 subjects will be assigned to one of two treatment groups (JNJ-38518168 100 mg/day [n=60] or placebo [n=30]) and will receive study medication for up to 12 weeks.
At any point during the study, the subject*s dose may be decreased to 50 mg daily, if in the opinion of the Investigator the 100 mg dose of JNJ-38518168 is not well tolerated.
There is a 4-week follow-up period after dosing is complete. A substudy in detecting biomarkers in synovial biopsy tissue will be performed at selected sites in approximately 18 subjects (JNJ-38518168 100 mg/day [n=12] or placebo [n=6]).

A Data Monitoring Committee (DMC) composed of sponsor clinicians and

statisticians and/or other individuals not associated with the conduct of the study will review study data for safety purposes on an ongoing basis. Interim analyses of unblinded data will be performed and then reviewed by the DMC on two occasions: safety data when approximately 20% of subjects complete Week 12, and safety and efficacy data will occur when approximately 50% of subjects complete Week 12.

Intervention

DOSAGE AND ADMINISTRATION
Each subject will receive one of the following treatments:
* JNJ-38518168 100 mg once daily for 12 weeks
* Matching placebo capsules once daily for 12 weeks
Study drug will be provided in 50 mg overencapsulated tablets (capsules). All subjects will start at a dose of 100 mg qd taken in the morning on an empty stomach with water. The dose may be decreased to 50 mg qd, if the study medication is not well tolerated. The trial Medical Monitor must be notified of dose reductions. If a subject*s dose is decreased to 50 mg qd, it will remain at that level until the end of the study.

All Protocol Subjects
Blood samples will be drawn in all subjects at the times specified in the Time and Events Schedule for the following assessments:
* Measurement of biomarkers which may include but not be limited to inflammatory markers, autoantibodies, synovium/cartilage/bone markers and other categories of biomarkers potentially
involved in the development and the progression of rheumatoid arthritis or related to the JNJ-
38518168 mechanism of action.
* Microarray and RT-PCR analysis of RNA

Synovial Biopsy Substudy Subjects:
The following assessments will be performed at selected sites in a subset of approximately 18 subjects (JNJ-38518168 100 mg/day [n=12] or placebo [n=6]) at the times specified in the Time and Events Schedule:

* Synovial tissue samples collected via biopsy performed during the arthroscopy or ultrasoundguided biopsy of one or more of the inflamed joints.
* Synovial inflammation will be assessed via immunohistochemistry and digital imaging
analysis.
* RNA and epigenomic profiles will be analyzed in synovial tissues using microarray and other
technologies.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS
Exploratory PK/PD modeling may be conducted to evaluate the relationship between plasma
concentrations of JNJ-38518168 and efficacy scores such as DAS28, ACR response rates, and biomarkers.

PHARMACOGENOMIC EVALUATIONS
An optional pharmacogenomic blood sample (10 mL) will be collected to allow for pharmacogenomic research (where local regulations permit).

Study burden and risks

SAFETY EVALUATIONS
Adverse events and concomitant medications will be collected from the time of informed consent signing until study termination. Clinical laboratory tests, vital signs and 12-lead ECGs will be assessed throughout the study at time points specified on the Time and Events Schedule.
At any time following randomization, if a subject has an ECG with QTcF > 480 msec but < 500 msec, there will be a mandatory dose reduction to 50 mg qd with a repeat ECG one week later. In addition, study medication will be discontinued if there is an increase in QTcF interval [QT interval corrected using formula of Fridericia] to an absolute value > 500 msec or if there is a change of > 60 msec over the baseline interval (average of 3 ECGs at randomization) OR if there is a sustained QTcF interval > 480 msec but < 500 msec upon repeat ECG one week after dose reduction.

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

- Have a diagnosis of Rheumatoid Arthritis (RA) at screening established as positive for either anti-cyclic citrullinated peptide (anti-CCP) antibody or Rheumatoid Factors (RF) in serum at screening.
- Have active RA at screening and at baseline (for joint count only). Active RA is defined for the purpose of this study as persistent disease activity with both of the following criteria:
a. Serum CRP > upper limit of normal at screening only.
b. 66/68 Joint Count as follows:
* Primary study subjects: at least 6 swollen and 6 tender joints using a 66/68 joint count at the time of screening and at baseline
* Synovial biopsy substudy subjects: at least 4 swollen and 4 tender joints using a 66/68 joint count with a clinically inflamed knee or ankle joint at the time of screening and at baseline.
- Have been treated with and tolerated MTX treatment at dosages between 7.5 to 25 mg/week inclusive, for a minimum of 4 months prior to Screening and must have a stable MTX dose for a minimum of 4 weeks prior to the first study drug dose.

Exclusion criteria

- Have a diagnosis of Rheumatoid Arthritis Functional Class IV according to the American College of Rheumatology criteria which has been ongoing for at least 6 months prior to the first dose of study medication.
- Have inflammatory diseases other than RA, (including but not limited to ankylosing spondylitis, systemic lupus erythematosus, and Lyme disease).
- Have current signs or symptoms of liver or renal insufficiency or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances that are severe, progressive or uncontrolled in the Investigator*s

discretion.

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):	01-09-2009
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	JNJ-38518168
Generic name:	JNJ-38518168

Ethics review

Approved WMO Date:	08-07-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2009

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2010
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	EUCTR2009-012118-27-NL
CCMO	NL28359.018.09