A randomized, double-blind, placebo-controlled, phase 2a study of the efficacy, safety, and pharmacokinetics of MLN3897 in patients with rheumatoid arthritis taking methotrexate.

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

Summary

ID

NL-OMON30310

Source
ToetsingOnline

Brief title
C08005

Condition

- Autoimmune disorders
- Joint disorders

Synonym
arthritis, chronic joint inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Millennium Pharmaceuticals;Inc.

Intervention

Keyword: Chemokine blockade, Chronic Inflammation, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary endpoint for efficacy will be the percentage of patients achieving

ACR20 at Day 84 in MLN3897 versus placebo-treated patients.

Secondary outcome

Secondary endpoints for efficacy are as follows:

* The percentage of patients achieving ACR50 and ACR70 at Day 84

* DAS28-CRP score and the change from baseline to Day 84 in DAS28-CRP score

* ACR-N at Day 84

* Change from baseline to Day 84 in individual components of ACR response

criteria assessment score

* Time to ACR20 response

Study description

Background summary

Reumatoid arthritis (RA) is a chronic inflammatory disease primarily involving the joints. Pain and stiffness cause disability in RA patients. Moreover, the inflammation can cause joint destruction, leading to permanent disability. There is no cure for RA. Certain available therapies can decrease inflammation and slow progression of joint destruction. However, these therapies do not work for all RA patients. New therapies against RA are therefor required.
The inflamed synovial tissue of RA patients is characterized by large numbers

of immune cells. Chemokines facilitate the influx of these cells into the joints. The aim of the agent under investigation in this study (MLN 3897), is to block chemokine function.

Study objective

This is the first study of MLN3897 in any disease population. It seeks to establish:
1) The ability of MLN3897 to modify the signs and symptoms of RA.
2)The safety and tolerability of MLN3897 in combination with MTX.
3)The PK/PD profile of MLN3897 in the RA population, and comparison to that in the healthy volunteer population with respect to CCR1 receptor blockade.
4) MTX PK and MLN3897 PK and PD when these drugs are used in combination.

Study design

This phase 2a, double-blind, placebo-controlled, randomized study will be conducted in approximately 186 patients with RA who are taking stable doses of MTX yet continue to manifest evidence of active disease. All patients will be required to have been receiving MTX for at least 6 months prior to study entry and at stable doses of 7.5 mg to 25 mg for at least 6 weeks prior to enrollment. The main study will include a screening period, a 12-week active treatment period with 5 study visits (Days 1, 14, 28, 56, and 84), and an end of study (EOS) visit (30 days post-treatment follow-up visit [Day 114/EOS]).
All patients will be randomized 1:1 to receive either 10 mg MLN3897 or matching placebo on a daily basis from Day 1 through Day 83. Patients will continue throughout the entire study to follow their once-weekly MTX dosing regimen.
Of the 186 RA patients, a subset of approximately 16 evaluable patients (12 patients in the MLN3897 + MTX combination arm, and 4 in the placebo + MTX arm) will participate in intensive PK sampling for determination of MLN3897 and MTX PK. This subset of patients will be screened for eligibility during the screening period, have 8 study visits (Days -1, 1, 14, 27, 28, 29, 56, and 84), and an end of study visit (30 days post-treatment follow-up visit [Day 114/EOS]).
See protocol page 42.

Intervention

Patients will receive orally 10 mg MLN3897 or matching placebo once daily for 83 days starting on Day 1.
All patients will take MTX orally every seventh day at their previously established stable dose. Patients participating in the PK substudy will be instructed to synchronize their weekly dosing of MTX with the clinic visit schedule.

Study burden and risks

* QT interval prolongation.
* A greater chance of getting an infection or difficulty fighting off an infection
* Decreased visual function
* Nausea, vomiting, constipation
* Mood changes, dizziness
* Blood in urine
* Abnormal lab results (for example increased blood levels of muscle or liver enzymes)

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

Patients should:

- Meet the ACR diagnostic criteria for RA
- Have a RA Global Functional Class of I, II, or III
- Be taking MTX for a minimum of 6 months before screening
- If taking oral corticosteroids, no more than 10mg/day and dose unchanged for at least 4 weeks prior to screening
- If taking NSAIDs, stable regimen that has been unchanged for at least 2 weeks prior to screening
- Have at lease 6 swollen joints and 6 tender joints + at least 2 of the following: Morning stiffness with a duration of at least 45 minutes, CRP > 1.5ml.dL or ESR at least 28mm/h

Exclusion criteria

Patients cannot:
- Be taking any DMARD other than MTX concomitantly or within 1 month prior to study enrollment.
- Currently being treated with TNF-antagonists. A wash out of 8 weeks is permitted.
- suffer from tuberculosis
- have a HIV, Hepatitis B or C infection
- Have evidence of an infectious or acute cardiopulonary process on chest X-ray completed at screening
- suffer from any other serious illness.

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):	01-06-2006

Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	MLN3897

Ethics review

Approved WMO Date:	29-06-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2007
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	EUCTR2005-006165-14-NL
CCMO	NL11208.018.06