

# **A phase 1, first human exposure, single dose, double-blind, randomized, placebo controlled trial to assess the safety, tolerability, pharmacokinetics and pharmaco-dynamics after oral administration of Org 48775-0 in healthy male volunteers in fasted and fed state, in female healthy volunteers, and in rheumatoid arthritis patients with active disease while on methotrexate treatment.**

Published: 03-12-2007

Last updated: 11-05-2024

Primary: To assess the pharmacokinetics and effects of single oral doses of Org 48775-0 in healthy male volunteers, post-menopausal women and RA patients. Secondary: To study the influence of Org 48775-0 on the PK of MTX in RA patients To explore gene...

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Autoimmune disorders
<b>Study type</b>	Interventional

## **Summary**

### **ID**

NL-OMON32271

### **Source**

ToetsingOnline

### **Brief title**

Phase 1 Org 48775-0

## Condition

- Autoimmune disorders

### Synonym

Rheumatoid arthritis

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Organon Nederland BV

**Source(s) of monetary or material Support:** Farmaceutische industrie

## Intervention

**Keyword:** MAPkinase inhibition, Pharmacodynamics, Pharmacokinetics, Safety

## Outcome measures

### Primary outcome

Pharmacokinetics of drug

Pharmacodynamics of drug (ao measurement of inhibition in TNF-release after ex-vivo LPS stimulation)

Routine clinical and lab parameters

### Secondary outcome

Transcriptomics / Proteomics

## Study description

### Background summary

Activation of the p38 mitogen activated protein kinase (MAPK) pathway plays a crucial role in the production of the proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ . Current approaches with biologicals that block the effect of both cytokines are efficacious in both animal models and in the clinic for

auto-immune diseases.

Another therapeutic option would be the inhibition of MAP-kinase of which four variants are known among which p38 $\alpha$  is considered to be the most relevant variant involved in inflammatory responses. It plays an important role in the pro-inflammatory activation of e.g. monocytes and macrophages, lymphocytes, neutrophils and endothelial cells. Many different stimuli can activate p38 $\alpha$  MAPK, including LPS and other bacterial products, cytokines, growth factors, and stress signals such as heat shock, hypoxia, and ischemia/reperfusion. The p38 $\alpha$  MAPK positively regulates a variety of genes involved in inflammation. For its broad pro-inflammatory role in several in vitro systems, inhibition of the p38 $\alpha$  pathway has been advocated as a novel therapeutic strategy for inflammatory diseases such as RA.

Org 48775-0 is a potent and selective p38 kinase inhibitor that in addition may be involved in reduction of pain, not solely as a result of reduction of inflammation but also via direct interference of the mechanistic role of p38 kinase in pain signaling. As the pre-clinical experiments have not raised safety concerns precluding administration of Org 48775-0 to humans, this protocol describes the plan for the first study with the compound in humans. This will concern healthy male volunteers, post-menopausal women and RA patients who are given single doses, and healthy male volunteers in whom the effect of food intake will be investigated.

## **Study objective**

Primary:

To assess the pharmacokinetics and effects of single oral doses of Org 48775-0 in healthy male volunteers, post-menopausal women and RA patients.

Secondary:

To study the influence of Org 48775-0 on the PK of MTX in RA patients

To explore gene expression and proteomics after administration of Org 48775-0 in the 3 populations

## **Study design**

Randomised , placebo-controlled, double blind, dose-escalation interventional trial

## **Intervention**

Healthy male volunteers: Single oral dose(s) of study drug in an escalating dose design with randomised placebo

Healthy post-menopausal females: Single oral dose of study drug

Patients: Single oral dose of study drug

## **Study burden and risks**

MAPkinase is essential in host defense and excessive and long-lasting inhibition is associated with impaired host defense. In this trial this may occur, but that is unlikely as the trial is designed such that excessive and long-lasting inhibition of MAPkinase are unlikely to occur. This was achieved by using not only classical ways to determine the starting dose but also the MABEL approach using data on the in-vitro inhibition of the compound assessed in human blood.

The drug is further potentially associated with phototoxicity and the subjects are requested to avoid direct exposure to sunlight.

Because of the limits defined for MAPkinase inhibition (that are known to be well tolerated by healthy subjects and patients) the risks are considered to be limited. As CHDR is closely linked to LUMC, also in the case that problems should occur, it is considered that these problems can be adequately managed.

## Contacts

### **Public**

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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 volunteers: healthy

Female volunteers: healthy and post-menopausal

Patients: active disease and treatment with MTX

## Exclusion criteria

Volunteers: clinically significant abnormalities (females: possible fertile)

Patients: clinically significant abnormalities (females: possible fertile) and recent treatment with anti-TNF therapy

## Study design

### Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	20-12-2007
Enrollment:	50
Type:	Anticipated

## Ethics review

Approved WMO	
Date:	03-12-2007
Application type:	First submission

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	
Date:	21-01-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	
Date:	07-04-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	
Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	
Date:	15-09-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	
Date:	06-10-2009
Application type:	Amendment
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**

EudraCT

CCMO

**ID**

EUCTR2007-001993-10-NL

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