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.

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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 patientsTo explore gene...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	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 annd 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-1β and TNF-α. 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 p38α 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 p38α MAPK, including LPS and other bacterial products, cytokines, growth factors, and stress signals such as heat shock, hypoxia, and ischemia/reperfusion. The p38α MAPK positively regulates a variety of genes involved in inflammation. For its broad pro-inflammatory role in several in vitro systems, inhibition of the p38α 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 trail 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

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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	ID
EudraCT	EUCTR2007-001993-10-NL
CCMO	NL20500.058.07